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AND ABSTRACT OF THE LITERATURE

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HONORARY CONSULTING EDITOR
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Cardiac Disease in its Relation to Industrial Efficiency

Chronic Manganese Poisoning: Two Cases

Trinitrotoluene Poisoning
Its Nature, Diagnosis, and Prevention

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THE PROBLEM OF HEART DISEASE IN THE INDUSTRIAL WORKER*

PAUL D. WHITE, M.D.

Boston, Mass.

HEART disease and industry are not incompatible. An individual may be productive even while bedridden with heart trouble a large part of the time. The active trained mind of a cardiac cripple may be more valuable in industrial progress than a body in perfect health controlled by a dull intellect. In general, we have been inclined to shelter too much our young patients with heart disease. They can usually do more than we have permitted. An example of the interest expressed in their own future as a group is a letter which I received recently from a young man 20 years of age who has been crippled since childhood by rheumatic heart disease, and for that reason unable to obtain all the education which he desired, and who is now facing the need of supporting himself without the best training for a clerical job. He is unable to do hard physical work and cannot obtain even light work because of the stigma of his heart disease. His plea for the future of the whole group of young people with heart disease overshadows all the rest of his letter. He is a champion of their cause.

There are two problems of heart disease in industry: first, that of the individual worker; and second, that of the attitude of industry in general. My subject is concerned particularly with the problem of the individual, but in closing I shall discuss briefly the general relation of industry to heart disease.

THE INDIVIDUAL WORKER

Every industrial worker with heart disease is a problem in himself. The solution of each problem depends on the answers to two short questions: How much work can the individual do? What is his future? If we can puzzle out the answers to these questions, we can solve the problem of heart disease in the individual industrial worker. The first question is a relatively easy one — to be ascertained at once by questioning the subject, by suitable tests, or by observing the subject while at work. The question would be better put as follows: How much work can the individual do without discomfort? — for sometimes a

* Read before the Health Service Section at the Tenth Annual Meeting of the National Safety Council, Boston, Mass., Sept. 29, 1921. Received for publication Oct. 17, 1921.

person will force himself to do work often very distressing and even injurious to himself.

The other question at times is a very difficult one to answer for the future of the individual depends on a number of factors. In the first place, a correct diagnosis is of prime importance, and yet is very often neglected. Symptoms of heart disturbance, such as palpitation (that is, the disagreeable sensation of the heart beat), pain in the region of the heart, and shortness of breath, do not by any means always signify heart disease. Nor do fainting attacks or weakness indicate heart disease. Nor do murmurs or rapid heart action mean a diseased heart. And yet I have often seen patients diagnosed by themselves, by their relatives or friends, or, not infrequently, even by their physicians as having heart disease, when to all methods of examination their hearts appear normal. This has been true in 60 out of 250 cases which I have seen in consultation (24 per cent.) in the last two years. To be sure, some of these people are incapacitated by their symptoms even though their hearts are normal; the nervous system or thyroid gland may be at fault. Though it may be impossible for such individuals to carry on ordinary work, the heart should not be blamed and treated, and cardiac statistics padded by these thousands of cases. The very first step in our problem, therefore, is to make a proper diagnosis. This having been made in its entirety, the rest, even the forecast of the future, is not difficult. The other important point in answering the question as to the future of a given case is the study of the individual's reaction to medical treatment or to a definite test of work over a given interval of time. An hour, a day, or a week may suffice to answer this.

Diagnosis. — Let me now take up these two steps — diagnosis and reaction to work — in more detail, since they are so vital in judging a case. Recently, diagnosis in heart disease has been put upon a sound basis, and I shall discuss briefly the system as it is now in use in the Heart Clinic at the Massachusetts General Hospital and, in somewhat similar form, in some other hospitals and cities. Because it is not widely used and because it has proved so useful, I wish to emphasize it in its value in the industrial health problem.

In former times, and not so far back either, as any one who received his medical diploma ten years or more ago will testify, heart disease consisted of mitral regurgitation and other such valve damage. A little was said about enlargement, myocarditis, and pericarditis. Disturbances of rhythm were beginning to be recognized in a hazy way, very shortly to flash up and take the lead for a while, with such diagnoses as heart block and auricular fibrillation (absolute arrhythmia) sufficing as diagnoses of heart trouble. At this same time Mackenzie's teaching of myocardial capacity was filtering in here and there, taught in a very disjointed way, unconnected with structural or etiological condition. Now, more than ever before, we see the tremendous importance of the cause of heart disease as a vital part of our estimate of the heart's condition and particularly of its future. Finally, at the present moment the best diagnosis we can make comprises all three factors — the cause of the trouble (or etiology), the degree of anatomical damage, and the extent of functional impairment. Unless all these three points are studied and stated, I consider the diagnosis of a case of heart disease inadequate. By using this method not only do we have a clear picture of the individual at the present time but also a very solid foundation for a prophecy as to his future.

Each diagnosis should include, then, all available information as to etiology, structure and function. If the cause of the heart disease is unknown, it should be so

stated. Such a declaration of our ignorance will stimulate us to study the individual further and to search more deeply into the causes of heart diseases in general.

The most common causes of heart disease are arteriosclerosis and rheumatic fever with its allied infections, such as chorea and tonsillitis. Syphilis and thyroid disease are other important causes. It is of much value in estimating the future of a person with heart disease to know what caused the disease. For example, given three hearts with organic defects of equal degree, the future is as a rule much brighter if the cause is rheumatic fever than if it is arteriosclerosis or syphilis. Until recently syphilitic heart disease carried with it an especially bad outlook — indeed, it was often only a question of a few more months of life. Now, under better treatment, the future is not quite so dark.

The next step in diagnosis is the determination of the actual degree of anatomical change so far as possible — the size of the heart, the valve changes, the involvement of the pericardium and the presence of disease in the aorta. Careful physical examination, supplemented if necessary by X-ray and electrocardiographic studies, will give a fairly good answer to this part of the problem.

And then finally we come to a very vital part of the diagnosis — the functional condition of the heart. Are there actual signs of heart failure, such as swelling of the feet, or is there severe heart pain or shortness of breath in the presence of a damaged heart? If so, there is heart failure — that is, decrease in cardiac capacity far below what it should be. We speak of the type of failure with the shortness of breath and edema as the *congestive*, and the type of failure with heart pain as the *anginal*. Both are significant of serious heart damage and weakness. Of course, there may be much heart disease without failure, but sooner or later in such hearts failure is apt to appear. All gradations of functional limitation of the heart's capacity exist, and following more or less one of the classifications of the New York Association of Cardiac Clinics we may speak of five groups of individuals with heart disease as follows:

1. Those able to carry on their habitual activities (without symptoms of distress);
2. Those able to carry on slightly curtailed activities;
3. Those able to carry on moderately decreased activities;
4. Those able to carry on only greatly diminished activity;
5. Those unable to carry on any of their habitual activities.

Finally, under the heading of functional diagnosis are to be included the disturbances of rhythm, rate and pressure, such as heart block, auricular fibrillation, hypertension and pulsus alternans.

A few examples will suffice to show the usefulness of this scheme of diagnoses. Take first a man 35 years of age who has a crippled heart following tonsillitis and rheumatic fever twelve years before. His heart condition has been diagnosed as a leaky valve. After he has been carefully examined the following diagnosis is made: "Rheumatic heart disease with aortic regurgitation and slight mitral involvement, cardiac enlargement, with normal rhythm and able to carry on habitual activities without symptoms." Now such a young man, although he has a loud murmur, may be able to live an active, useful life of many years; only late in life may symptoms of heart failure appear. The fact that rheumatic fever was the cause of his disease, the fact that his aortic valve is involved with little damage to his mitral valve (mitral stenosis would be more serious), the fact that he has a regular pulse, and, finally, the fact that he has no symptoms of heart failure make such a young man a good risk for the future. The only things which we must do with regard

to him are to be sure that his tonsils are removed if they are in the least diseased or if there is the slightest doubt as to their condition, and to avoid so far as possible further rheumatic infections (as a matter of fact best done by the tonsillectomy itself). There are many young people with heart trouble who are now being condemned as invalids and useless because they happen to have loud murmurs, about whom one may be as optimistic as I have indicated above.

Take another man, 42 years of age, who is beginning to have heart pain on exertion. He boasts, perhaps, that he never was sick in his life, but on careful questioning he admits that he had a venereal sore fifteen years before. On examination one finds his heart enlarged, with a slight but definite degree of aortic regurgitation, and a positive Wassermann reaction. His case is diagnosed as, "Syphilitic heart disease with aortitis, aortic regurgitation, cardiac enlargement and normal rhythm, able to carry on slightly limited activity." In spite of the fact that he may appear to be a robust man and may have only a slight aortic murmur, his future is very serious at the present stage of our medical knowledge. This is all due to the fact that syphilis is the cause in this instance, and not rheumatism. Once upon a time both of these men, the one of 35 and the one of 42, would have been classed simply as cardiacs with aortic regurgitation, the younger man with more marked valve damage than the older.

Finally, let us suppose another man, one 27 years of age, with shortness of breath and palpitation on moderate exertion and occasionally when excited. His symptoms are worse than those present in either of the two cases already cited. He gives a past history of the usual children's diseases without rheumatic fever or chorea. He has always been high-strung as his father was before him. His father is alive and well at the age of 64 years. The patient broke down at the front during the war after a long bombardment of his trench by the enemy. He was said at the time to have "disordered action of the heart," and has been more or less incapacitated since. People are afraid to give him work because of his symptoms and history; yet he is well educated and bright. His diagnosis is, "Nervous heart with no evidence of heart disease." He has a rapid heart beat at times of examination, and under strain is unable to carry on his ordinary activities as well as normally. Now such a man may be very valuable in industry. He is apt to be very quick to learn some delicate or intricate work and may accomplish much more in the end than his husky, stolid comrade who can do a hard day's work with the pick and shovel but who rarely has an idea pass through his brain. Let us remember this large group of keen, nervous individuals who cannot stand a hard strain but who are able none the less to accomplish a great deal. Such young men and women, in spite of their symptoms, will undoubtedly outlive the men with syphilitic and rheumatic heart disease. Our chief concern in such cases is to protect the sensitive nervous system. The heart is sound enough.

These three examples are, I believe, enough to show the great importance of establishing a correct and complete diagnosis in each employee with heart disease. Sometimes a case is baffling, but if so, let us confess it and closely follow the individual until we can arrive at the correct conclusion, if it be possible.

Functional Tests. — After the diagnosis has been determined, the other essential point in the proper estimation of a person's capacity and future is the actual test. Many articles have been written about testing the heart's function and some facts of value can be extracted from them. We must realize, however, that in a given case it is not the cardiac function that we meas-

ure with all our tests but the physical fitness of the individual as a whole. His nervous system plays a part in his response to the tests as well as his heart and other muscles. The reaction of the pulse rate, blood pressure, respiratory rate and general condition to measured exercise, such as stair climbing, hopping on one foot, running a given distance and swinging dumb-bells, has been studied and all these exercises have their advocates. Dr. May Wilson (1) of New York has been attempting to find the "equivalent of ordinary exertion" by standard tests — particularly dumb-bell swinging. Two iron dumb-bells swung from the floor to full stretch of arms overhead and back again between the legs at a constant rate of two seconds for each swing were used in testing children from 6 to 15 years of age. The weight of the dumb-bells varied from 3 to 20 pounds, and the number of swings from ten to thirty. Thus, in her classification, mild exercise for the children of from 6 to 8 years consisted in swinging two $1\frac{1}{2}$-pound dumb-bells ten times, while strenuous exercise for children of from 12 to 15 years consisted in swinging two 10-pound dumb-bells thirty times. Now by carrying this or some similar test a step further we may roughly correlate it to industry. If the measurement of physical action in a certain occupation can be figured in foot-pounds or kilogram-meters per unit of time, we may be able to arrive at some sort of estimate of the cardiac ability, *always included in the general fitness of the individual*, by the test of a like amount of work in a unit of time in dumb-bell lifting.

Papers by Barringer (2) (3), Rapport (4), and Mann (5) have in the last few years taken up the question of the significance of blood pressure and pulse rate changes in man after exercise tests, particularly the dumb-bell test.* Conclusions to be drawn from their work are that the pulse rate changes following exercise are unreliable as evidence of circulatory condition, but that the systolic blood pressure curve is of some value in judging limitations of physical capacity, not of cardiac capacity. Rapport, in working with Lewis, showed that "as an immediate sequence of accomplished exercise, whether that exercise is moderate in degree, or whether it calls forth a full effort on the part of the person who performs it, there is a rise of systolic blood pressure." In criticizing Barringer's reliance on a delayed rise as indication of limitation of cardiac capacity, Rapport quite rightly says:

> To speak of the rise ("delayed rise") itself as an index of a change in the circulatory reaction is, in the light of our experiences, unsound; to speak of a delay in the full development of the rise ["delayed summit"] with severe effort, is usually to speak correctly. . . . The work done by the heart in the intact and sentient animal at rest has never been accurately computed; still less has the *capacity* of the heart for work in circumstance of overload. It has become fashionable, nevertheless, to express the capacity of the heart for work in terms of measure, terms which do not measure that capacity, but something which is quite different. . . . A curve of systolic blood pressure during or following exercise may be an exact expression of real events; but these events are blood pressure events and the measure is of blood pressure and not of cardiac work [or cardiac capacity].

Nevertheless, it is true that as the degree of exercise done approaches the limit of an individual's physical capacity, *whether he be normal or affected with heart disease*, the rise in blood pressure following the test shows a more and more delayed summit. With the extreme in delayed summit in a given person go symptoms of distress — dyspnea and exhaustion. Right here it should be said that a healthy person untrained may show this sign and these symptoms with considerably less exercise than a person with heart disease who shows

* Lifting a 25-pound bar over the head is a useful variation of the dumb-bell test.

no failure and who has excellent reserve power.

Two examples of the systolic blood pressure exercise test will make clear some of the points just mentioned. The man 35 years of age (and 150 pounds in weight) with rheumatic heart disease and aortic regurgitation, whom we have already cited, is examined at rest for fifteen minutes before the exercise. His blood pressure, at first 130 mm. Hg. systolic, becomes on the second measurement 120 mm., and is thereafter fixed at 120 mm. His pulse rate before the exercise is steady at 76. He is then put through the test consisting of swinging two 10-pound dumb-bells thirty times from the floor above the head at the rate of one swing every two seconds. He shows slight breathlessness and weariness at the end of the exercise; his pulse rate is 108 and his systolic blood pressure 140 mm. Hg. thirty seconds after the exercise is stopped. (Ten seconds after the exercise the systolic pressure is 130 mm.) One minute after the exercise the blood pressure becomes 135 mm., and the pulse rate 90; and at the end of two minutes the pressure is 125 mm. and the pulse rate 70. This is quite a normal reaction.

For the second case let us take the man 42 years of age with the syphilitic heart disease and aortic regurgitation, whom we have also cited. He is put through exactly the same exercise as the previous man but complains of considerable precordial pain and is very breathless at the end of the exercise. His systolic pressure has gone up from his normal pressure of 130 mm. to 145 mm. at the end of one-half minute, to 160 mm. at the end of one minute, and stays at that point after one and one-half minutes. At two minutes the pressure is 150 mm., and at three minutes 140 mm. His pulse rate, at first 80, becomes immediately after the exercise 160, at the end of one minute 140, and at the end of two minutes 100. It is obvious that the test more than taxed the strength of this man. The delayed summit of the systolic blood pressure is here well marked.

Certain factors enter into such exercise tests, however, that render them imperfect. In the first place, muscles may be in use quite different from those exercised in the particular occupation; secondly, there is an added strain due to nervous excitement at the time of the test; and, thirdly, the test lasts but a few minutes at the most, while the job in question lasts several hours every day. Thus, only a very rough estimate of individual physical and cardiac ability can be made from such tests. Stair-climbing, running and hopping are all open to the same objections.

There are no short cuts to determining the heart's power that I know of which are of universal value. Respiratory tests have been suggested, such as the length of time the breath can be held, the height to which a mercury column can be blown, the length of time the mercury column can be maintained at a certain height, and the vital capacity. As in the case of the exercise tests, if these are normal the individual's heart cannot be in a very bad condition. The vital capacity test, which is the measurement of the amount of air that can be expired after a full inspiration, and the test of holding the breath are useful measures of the degree of heart failure present. Vital capacity and the power of holding the breath are also reduced in marked psychoneurosis (6). Similarly in these conditions the carbon dioxide rebreathing test shows a capacity below normal. But the only sure way to determine whether a man with heart disease can stand a certain job is actually to try him out at it. No two jobs are exactly alike and no two individuals have exactly the same kind or degree of heart disease. A few minutes, a few hours, or a few days at the most will answer our question. Having by observation, examination and some simple test roughly deter-

mined the fitness of the individual, the exact measurement of his strength, cardiac and general, in relation to a certain job must come from the job itself. We must remember, moreover, that it is possible to train a man for a job physically as well as mentally though he appear incapable at the first trial. There are occupations for all kinds of cardiac cripples. A man unable to climb a flight of stairs without shortness of breath is obviously unfit to work as a freight handler, but he may prove very useful in keeping the office files. A concise folder has been published recently by the Association for the Prevention and Relief of Heart Disease (7) giving lists of occupations — both skilled and unskilled — generally suitable for people with heart disease. This folder can, I believe, be obtained on request from the office of the Association at 325 East 57th Street, New York City.

General Relation of Heart Disease to Industry

Having finished this brief discussion of the problem of heart disease in the individual worker, I should like to conclude with a few remarks on the problem of the relation of heart disease to industry in general. In the first place there is not, so far as I know, any industrial heart disease. There is, of course, effort syndrome, but for that industry is not to blame. The relation of industry to the production of arteriosclerosis is still a question to be solved. Arteriosclerosis is a very important cause of heart disease as I have said, and if years of hard work produce arteriosclerosis, then industry may be accused of causing heart disease. The factors of the individual's susceptibility to arteriosclerosis, of the exciting effect of hard physical or mental work, and of the time element of hours of work per day or week must eventually be studied and weighed before we can point out how industry may be relieved of the possible blame of inducing arteriosclerosis.

In helping to eradicate heart disease, industry should insist on the proper physical examination of the worker. If the tonsils are diseased, their early removal may prevent rheumatic heart disease or prevent the increase of such disease if already present. It is very worth while to try to eradicate rheumatic fever for it is one of the serious scourges of the youth of the land. If there is a history of syphilis, or if the Wassermann reaction is positive, proper intensive treatment may prevent syphilitic heart disease. Proper education and campaigning against venereal disease (including the adoption of prophylaxis if necessary) will also help, for syphilitic heart disease, as I have already said, is a very serious matter. Early recognition and treatment of thyroid disease may avert thyroid heart complications. Avoidance of long-sustained excessive physical or mental effort, and the insistence on regular periods of relaxation should reduce the degree of presenile arteriosclerosis.

People should, on the average, live far longer than they do, though the 300 years of age advocated by the Barnabas Brothers in Shaw's *Back to Methuselah* is a bit too great a jump from our modest three score and ten to accomplish at the moment. To increase the average life, infectious disease must be eradicated, cancer overcome, and accidents and the strain of work reduced. There is, in general, too high a tension in American life, both in work and in play. We do not sit long enough at the breakfast table or over the teacups — we might do well here to take a leaf from the leisurely ways of the European. An engine run at high speed all the time wears out too quickly. The human machine, too, is liable to break down eventually with accident to the heart or brain.

Not only may industry do its share in the prevention of heart disease but it may also do its part in the prevention of heart failure in the individual worker who has heart dis-

ease. The tremendous improvement in the care of the health of workers carried out by industrial concerns all over the country makes it possible to check up frequently the physical condition of the worker with heart disease. By examinations given weekly or monthly or at intervals as circumstances demand, the earliest symptoms or signs of failure may be detected and proper recommendations as to treatment given. Rest in bed for a day or two at such a time may save the individual weeks of illness and loss of income later. It may prove to be very valuable insurance. Some of the cardiac clinics in New York meet on Friday evenings so that their patients may be advised to stay in bed for the week-end if necessary, with little or no loss of time from their work.

A word should be added concerning the need of special vocational training of young people with heart disease so that they may be able to support themselves comfortably later in life in occupations which will not involve physical or mental strain. Special classes have already been instituted in connection with the public school system of New York City with this aim in view.

Finally, let me repeat that heart disease and valuable productive ability may coexist in the same individual. We must know the kind and degree of the heart damage. Knowing this, we should be able properly to place the worker by using our common sense, by tests for a rough estimate of the physical capacity of the individual, and, finally, by the actual test of the work itself.

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CARDIAC DISEASE AND ITS RELATION TO INDUSTRIAL EFFICIENCY *

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AT a time when we are taking stock of our resources and looking for means of increasing the national output by reducing our losses from disease, it behooves us to study not only the mortality records but also such figures as are available to tell us what diseases cripple men and women and lower their standard of efficiency. The best figures to which we can turn for such information are those supplied by the Ministry of National Service and drawn from their recruiting experiences. From the tables which they have published, it appears that about 10 per cent. of the men rejected as unfit for military service were rejected on account of valvular disease of the heart. In some districts, indeed, this kind of disability was responsible for more rejections than any other. This figure is to some extent discounted by the fact that cardiac murmurs were too readily received as evidence of valvular disease by recruiting authorities, the result being that many men who might have made efficient soldiers were rejected on inadequate grounds. On the other hand, we have to recollect that of the four great causes of organic heart diseases — to wit, rheumatic infection, syphilis, high arterial tension, and "senile" arteriosclerosis — the first alone finds a large proportion of its victims among persons of military age. The others fall with heavier incidence on men past the age of 40. Moreover, it must be remembered that rheumatic heart disease attacks women rather oftener than men. It is therefore clear that cardiac disease is responsible for a very great wastage of the nation's strength.

It is scarcely necessary to impress upon the medical profession the need for a more concerted plan of attack upon these diseases. Already, in America at all events, there are signs of such a movement. Nor should we expect or wish the profession to regard this attack on disease primarily from the commercial standpoint. Our chief motive for such an attack is, and always ought to be, the prevention and relief of suffering. But it is nevertheless needful to impress upon those who must find the money essential to such a campaign, that the study of disease and its causes will pay its own way, not at once, of course, but as the years and decades go by, with unfailing certainty.

What, then, is to be our plan of campaign? Let us first review the objectives, and then pass to a brief consideration of strategy. In any attack upon disease the first objective must always be out-and-out prevention. Where prevention is not possible, we must fall back upon plans for the arrest of disease. Finally, in cases of severe and established disease, we must have plans for treatment, and these must include economic treatment.

First, how is cardiac disease to be prevented? There is no disease that needs more time and energy devoted to the study of its causes than does cardiac disease. Even if the belief, which I share, in the streptococcal origin of rheumatic heart dis-

* Received for publication May 2, 1921.

ease be accepted, we are still far from knowing much about the influence of such matters as climate, soil, density of population, and so forth, on its initiation. Thanks to a grant from the University of Bristol Colston Research Society, and to the help of Dr. D. S. Davies and his clerk, Mr. W. N. Brown, I have been able to make an investigation into the incidence of rheumatic heart disease, based on the mortality records of Bristol. The results of this research have already been published,* and I am looking forward to an extended inquiry into the same matter on a basis of data more reliable than those furnished by death certificates. Even in cardiac syphilis, where so much is known as to the exciting cause, how little is known as to those factors which predispose to the incidence of the infection on the heart rather than on some other organ! And when we turn to those forms of cardiac disease which are related to high arterial tension or arterial degeneration, or both, it must be confessed that our study of their causation is little better than a mass of conjectures.

I do not believe that we can get far in these researches into the factors predisposing to disease without enlisting the help of every medical practitioner. Before this can be done, however, medical men must be trained to think etiologically in the matter of heart disease. If we consult any of our textbooks of medicine, we find that the pages devoted to cardiac disease are divided into paragraphs on "mitral regurgitation," "heart block," and so forth — titles which describe symptoms, not diseases. Not until they are replaced by such headings as "cardiac rheumatism," "cardiac syphilis," and so forth, shall we get students and practitioners to think of cardiac disease as something with a tangible beginning, a plant which ought not merely to be nipped in the bud, but actually to be prevented from getting any place whatever in the ground.

This kind of description of cardiac disease can only be built up on a systematic study of the whole subject. What is wanted is exhaustive examination of a large number of cases of cardiac disease, with careful records of the features of each, and classification into such etiological groups as I have already indicated. For example, we ought not to be content with recording such cases of cardiac syphilis as manifest evidences of heart block; every case of the disease ought to be studied with the electrocardiograph, and the presence or absence of block in its various grades noted. When all such information has been duly collected, it will be possible to write a connected account of each of the forms of cardiac disease, classified under headings which bear reference to causation. Then the medical profession will be armed with the information essential to a study of factors predisposing to cardiac disease, and we shall be able to get on with our task of finding out what those causes are. As I have already said, this can only be carried out by the general co-operation of the whole profession, and some better plan must be devised than the present one, by which family doctor, laboratory worker, and medical officer of health work separately from each other.

As to the second line of objective — arrest of disease in an early stage — there is little enough to be said, with one exception, and that relates to rheumatic heart disease in its childhood stage. The course of this disease is one of progress, not sustained or interrupted, but marked by a series of active phases, each lasting a few days or several weeks. In a certain percentage of cases the child is killed by the first of these phases. In a very few there is but one such phase, from which the child recovers, without further recurrence. In most cases the active phase of the disease

* Coombs, C. F.: The Incidence of Fatal Rheumatic Heart Disease in Bristol, 1876–1913. Lancet, 1920, **2**, 226.

recurs from time to time, each attack leaving the heart more damaged than before, so that the patient, if fortunate enough to survive into adolescence or adult life, finds himself handicapped at the outset of his wage-earning career by a crippled heart. Only too often his education has been so interrupted by the active phases, which keep him away from school, that he is fit for nothing but general labor. Ill equipped in mind, and dangerously crippled in body, he has little chance of doing any useful work. It would be well worth while to make some provision for his education to be carried on quietly during his periods of illness or, at all events, of convalescence — such provision as is being furnished in the analogous case of the tuberculous cripple. There is no reason why the same building that houses the latter, providing both treatment and education, should not be used for the rheumatic child also. Indeed, I believe that this is actually done at the Liverpool Country Hospital for children. The number of beds needed in each large city would not be great; one might begin with a dozen in Bristol, for example.

Arrest of other forms of cardiac disease in an early stage does not at present seem practicable, though it is possible that closer study of cardiac syphilis might discover evidences earlier than those at present known to us. Unfortunately, this and the arterial types of cardiac disease attack the patient when he has already reached or passed the watershed of life, so that his chance of effecting successful repair is small.

The third line of objective — better treatment of established disease — comes within the scope of this article only in its relation to the patient's capacity for work. One of the lessons of the war has been that many people with severe cardiac lesions can nevertheless do a surprising amount of work with impunity. Unfortunately, however, it is difficult for such people to compete in the open labor market with those whose hearts are sound. Employers are surprisingly considerate in such cases, but it is impossible, under the industrial conditions of the moment, to arrange for the interrupted work of these cripples in workshops and factories that are geared to run continuously at a high rate of efficiency. On the other hand, during the periods which many of them spend in the hospital, under observation, they have nothing to do, and this does no good to their morale. They would be better in every way if they had some kind of occupation. Workshops, similar to those provided for crippled ex-service men, ought to be attached to the hospitals so that these patients might be given an opportunity of combining productive work with institutional treatment.

In order to bring into being these proposals, little or no expenditure on building would be needful. All that is required in each large city, in each university city at all events, is that there should be such a rearrangement of the existing resources as to provide the team of practitioners specially interested in cardiac disease with a consultative out-patient department, hospital beds for the treatment of severe cases, and premises for the housing and treatment over long periods of such cases as I have alluded to in the two preceding paragraphs. The team must also have at its disposal such electrocardiographic and other apparatus as is needful for the careful and systematic study of cardiac disease. By this means knowledge will be gained which will be imparted to the students — the practitioners of the immediate future. Last but not least, this central organization must be in touch with the practitioners of the area. This will confer benefit in both directions — on the cardiac specialists, who would gain the breadth of view and sense of proportion that close attention to one branch of medicine is apt to impair; and on the general practitioners, who

would assimilate and apply each new discovery as it was made.

As an outcome of such co-operation it should be possible not only to diminish appreciably the sum total of human suffering, but also to effect such an economy of manpower as amply to repay the moderate outlay necessary for the initiation and maintenance of the organizations proposed in this article.

CHRONIC MANGANESE POISONING: TWO CASES*

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IT is the purpose of this paper to call attention to two cases of manganese poisoning occurring in steel workers who were engaged in handling manganese in the Bessemer process of making steel.

Manganese poisoning, though a comparatively rare finding, presents a symptom complex, definite and constant enough to be readily diagnosed, and should be suspected in workers handling manganese. This metal is used in the chlorine industry and to aid in liberating chlorine gas, in the liberation of oxygen, in dyeing, coloring glass, charging galvanic cells, in making lacquer, varnish and oil paints, enamel and linoleum, and in marbling soap. Manganese poisoning is also noted in workers in industries dealing with other metals or their ores, in which manganese exists as an impurity, and it was under such conditions that Casamajor (1) met his cases. Manganese is used extensively as an alloy with nickel and steel.

The number of cases of manganese poisoning is not large nor is there an extensive literature on the subject. Couper (2), in 1837, described characteristic symptoms in workmen in a chemical factory where manganese dioxide was ground in the manufacture of chlorine for bleaching powder. In 1901 (October 7), R. von Jaksch (3) described similar symptoms in three workmen employed as grinders of manganese dioxide, but diagnosed the findings as atypical cases of multiple sclerosis. H. Embden (4), in an article also published in 1901 (October 15), described characteristic symptoms in men employed in grinding manganese dioxide, and correctly diagnosed chronic manganese poisoning. In 1903 and 1904, respectively, Friedel (5) and Seiffer (6) reported cases which presented characteristic symptoms. Several years later von Jaksch (7) (8) and Seelert (9) summed up the fifteen cases of manganese poisoning in Europe described in the above-mentioned articles, and in 1913, Casamajor reported nine cases occurring in this country. In 1919, Edsall, Wilbur and Drinker (10) summarized the literature to date and reported the details upon three of the thirty cases which they examined.

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ETIOLOGY

The chief etiological factor by means of which manganese enters the system is undoubtedly coarse dust, though in the writers' cases fumes must have played a rôle. It has been pointed out by Oliver and others that most of our industrial poisonings are taken in the form of dust, and not so much the dust which is inhaled as that which is swallowed in the saliva. In his reports, von Jaksch stated that no new cases developed when the dust was abolished. Embden likewise ascribed his cases to manganese dioxide dust, as did also Casamajor and Edsall, Wilbur, and Drinker.

In order to supplement these clinical findings by analytical data, Reiman and Minot (11) made a study of the absorption and elimination of manganese ingested as oxides and silicates, in which they came to the following conclusions:

Ores containing manganese as oxides and silicates are soluble in gastric juice. Manganese is absorbed in the blood stream causing in most cases a slight temporary rise in manganese concentration followed by a quick return to normal. In none of the cases studied was the manganese content of the blood increased by the ingestion of manganese ores to a value more than double the normal level, and in some of the subjects no increase was noted. We suggest that individuals of the first group would probably be more susceptible to manganese poisoning than those of the latter.

Even prolonged feeding of large amounts of manganese ore to dogs failed to produce significant changes in manganese content of blood and tissues or to cause any pathological symptoms. Manganese ores are thus very non-toxic and in order to produce symptoms of poisoning must be ingested by individuals who are peculiarly susceptible. Clinical experience [10] has demonstrated that such persons are extremely rare.

Symptoms

Edsall, Wilbur and Drinker (10), who have made a careful review of the subject of manganese poisoning and have reported cases of their own, summarize the symptomatology thus:

As we have seen chronic manganese poisoning the following findings make the syndrome. We have numbered them in the most common order of appearance. It is difficult to emphasize in any written description the clearness with which the symptoms come out and the ease with which the diagnosis can be made.

1. A history of work in manganese dust for at least three months.

2. Languor and sleepiness.

3. Stolid, mask-like facies.

4. Low monotonous voice. Economical speech.

5. Muscular twitching, varying in degree from a fine tremor of the hands to gross rhythmical movements of the arms, legs, trunk and head.

6. Cramps in the calves and a complaint of stiffness in the muscles of the legs, the cramps usually coming on at night and becoming worse after a day of exertion.

7. Slight increase in tendon reflexes.

8. Ankle and patellar clonus. Frequently by stretching any of the muscles of the body it is possible to elicit rhythmical contractions. Romberg sign is inconstant; there is no incoordination.

9. Retropulsion and propulsion.

10. A peculiar slapping gait. The patient keeps as broad a base as possible, endeavoring involuntarily to avoid propulsion. The shoes are worn evenly and we have not been able to convince ourselves of the pronounced tendency to walk on the region of the metatarso-phalangeal joints, a feature strongly emphasized by von Jaksch [7].

11. Occasionally, uncontrollable laughter; less frequently, crying.

12. Uniformly absent are any disturbances of deep or superficial sensation, eye changes, rectal, genito-urinary or gastro-intestinal disturbances, reactions of degeneration, blood, urine, and spinal fluid alterations. It is significant that, unlike lead, manganese produces no life-shortening degenerations. Seriously poisoned men are long-lived cripples. The metal apparently makes a very definite attack upon some non-vital portion of the neuromuscular system, destroys it thoroughly, if time for action is permitted, and leaves the victim quite well in every other respect.

We have never seen either the salivation or edema described in foreign cases.

Pathology

The pathology of this condition is not clear. Von Jaksch reported that he never found any pathological lesions postmortem, but he does not state the details of his investigation. Casamajor had an autopsy in but one of his cases. He reported the appearance of degeneration in the longitudinal fibres of the pons in isolated bundles lying mostly close to the raphé. This degeneration was seen only in the pons. He was unable to reproduce it in rabbits or dogs.

Further autopsy studies of these cases would be desirable, but as the patients do not die of manganese poisoning *per se*, and as cases of the poisoning are comparatively rare, little is known of the pathology.

Treatment

Prophylaxis is the only hope in the treatment of chronic manganese poisoning. Inasmuch as dust was the means by which

poisoning occurred in the writers' cases, it is clear that, in order to remove all possibility of poisoning, dust must be eliminated from processes in which workers handle manganese. If this cannot be accomplished, the process should be rearranged or discontinued, as it was in the plant in question.

General eliminative measures by means of the kidneys, skin and intestines, etc., are indicated, but little is to be looked for in the way of improvement under such treatment.

Prognosis

In patients manifesting minor symptoms, recovery may take place. If, however, the patient has progressed to more advanced stages, the disease may be arrested, but a cure will not be forthcoming. The disease is not fatal, and the condition of the patient continues for months or years without change.

Report of Cases

The writers' two cases occurred in workmen who were occupied in the process of making manganese steel. A few words concerning the process may elucidate the environment in which they worked.

In the Bessemer process for making steel, molten iron from the blast furnaces is carried in large ladles to the converters, which are retorts shaped like an egg with a portion of the small end cut off. These converters are pivoted near the center and are so made that there are openings in the lower end from which heated gases may be blown through the molten iron, for the purpose of oxidizing a part of the carbon which is in solution in the molten iron. When this carbon is oxidized to a certain point, the resulting mixture is known as steel.

The molten iron from the blast furnace is poured directly into the opening in the top of the converter, after which the blast is turned on and the gases are forced through the molten iron. When the oxidation has progressed sufficiently, the blast is shut off and the converter is tilted so that the molten steel, which remains, runs from the opening in the top into a large ladle which is suitably placed to receive the steel as it pours from the converter. From this ladle the steel is withdrawn into moulds, and, after cooling, forms what is known as an ingot. The ingot is then made into the various shapes desired.

In the process of making manganese steel, manganese is added to the steel in a definite proportion and it immediately diffuses through the mass of steel. When the manganese is fused in the electric furnace, a definite amount of molten manganese is added to the steel and there results a product, the composition of which is uniform. Previous to the use of the electric furnace the solid manganese was added to the molten iron as it came from the blast furnace, and in the oxidation process a portion of the manganese was also oxidized, so that the resulting composition of the steel was not so definite nor so uniform.

In the operation of the electric furnace there are three large carbon electrodes, and the electric arc between these electrodes generates the heat which causes the fusion of the manganese. The electric furnace in use at the plant in question, when the two cases of manganese poisoning occurred, was a large steel chamber lined with firebrick and provided with two openings — one a sliding door (Figure 1*a*) through which the solid chunks of manganese were shoveled into the interior, the other a small opening connected with a spout (Figure 1*b*) from which the molten manganese was poured into a small ladle. The molten manganese in this small ladle was poured into the molten steel which had just been poured from the converter into the large ladle. When the sliding door was open for recharging the furnace, the heat within the furnace was

so intense that a considerable quantity of brown manganese fumes from the furnace escaped from the door into the surrounding atmosphere and entered the mouth, throat, and lungs of any person who was in the vicinity. Mr. S., superintendent of the

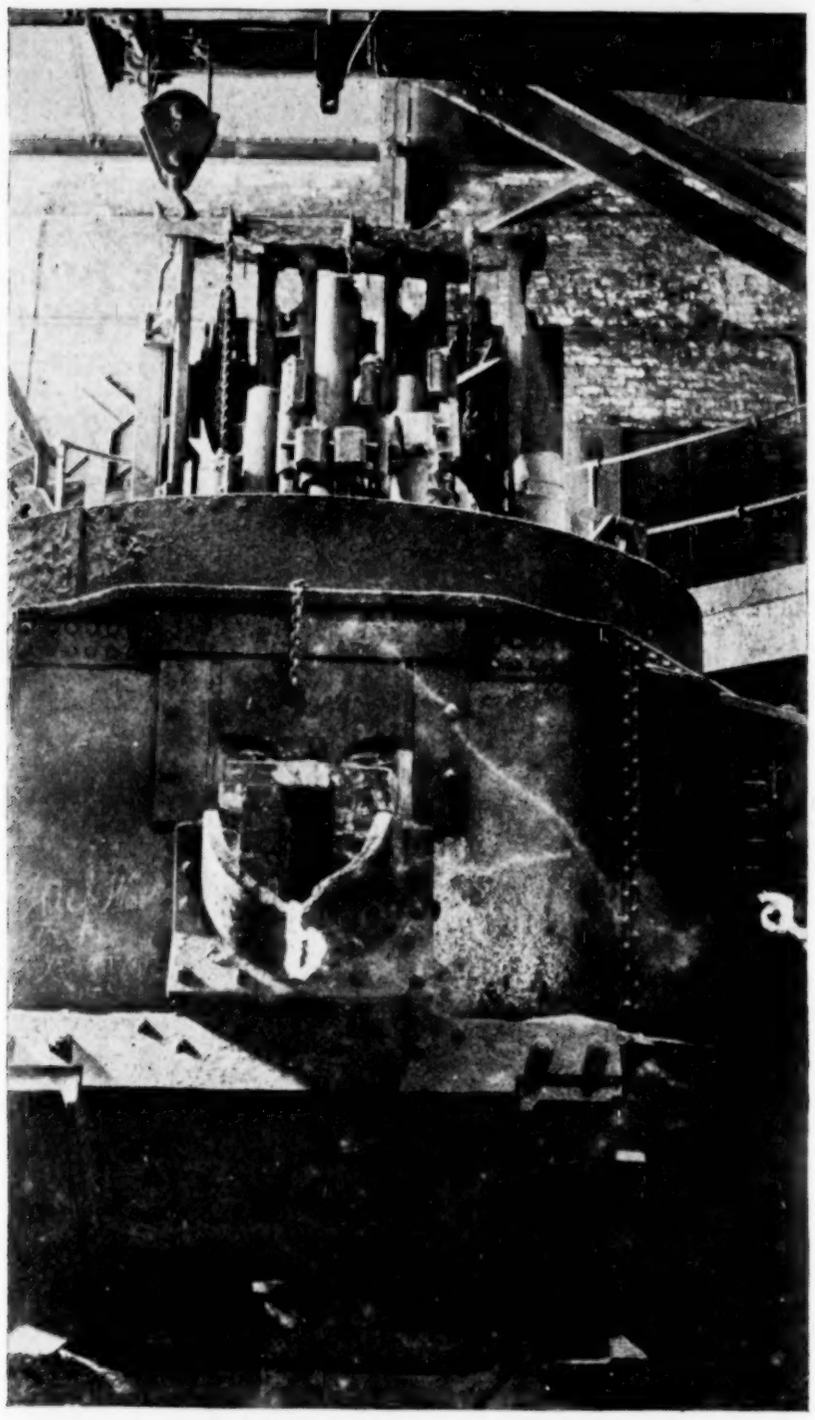

FIG. 1. — Electric furnace which was located in a room about 25 feet square.

(*a*) Charging door, into which the manganese was shoveled. At each charge the door was open long enough to allow 150 pounds to be shoveled in — about fifteen seconds — and during this time the fumes escaped freely.

(*b*) Spout from which liquid manganese was poured and from which fumes escaped in large quantities.

Bessemer department, stated that there was the same taste to the smoke that he had experienced when manganese had previously been ground and the dust had entered his mouth, and he believed that there was a considerable amount of manganese in the smoke which escaped. At his suggestion, therefore, the fumes from the electric furnace were analyzed, and were found to contain a high percentage of manganese, as did also the dust on the ledges in the same room. (See Table 1.)

TABLE 1. — ANALYSIS OF COARSE DUST AND FUMES FROM ELECTRIC FURNACE

Substance	Analysis of Coarse Dust from Electric Furnace	Analysis of Fumes from Electric Furnace
	%	%
SiO_2	17.14	23.38
Si	...	8.87
Carbon	17.18	19.30
Fe_2O_3	9.46	2.26
Al_2O_3	6.36	6.54
Mn	38.16	18.72
CaO	1.40	4.56
MgO	5.28	15.50
Phosphorus, As	0.13	...

Such was the environment in which were employed the two workmen whose histories are given below.

CASE 1. *History.* — N. V., an Italian, 25 years old, was examined first on Feb. 1, 1916, and subsequently at various times during the early months of that year. He gave the history of always being well and never having had any accidents or injuries or bad habits. He did not drink or smoke. He had been in this country ten years. He had been married four years; his wife had been previously married but had never had any children. He began working for the Steel Company on Sept. 25, 1912, as a laborer, and continued as a laborer until Feb. 16, 1914, when he was transferred to work as a charger at the electric furnace where ferro-manganese was fused before it was added to the converter to make manganese steel. He continued in this work until the time of examination when his foreman found it necessary to change his employment on account of increasing mental dullness.

Conversation with the patient and his wife brought out the facts that early in October, 1915 he began to be sleepy and indifferent, and that during Christmas week he took no interest in the festivities, which he had greatly enjoyed in previous years. Shortly after Christmas his wife noticed that he was often tremulous, especially at the table, that this condition persisted during sleep, and that he was rather disposed to stagger on his feet as though he were

drunk. Moreover, about the same time he would walk backwards and occasionally would fall backwards. Two or three times in succession, while trying to put up some window shades, he lost his balance, finally falling backwards to the floor.

Sometimes his wife noticed that his face was very red, and she said that it looked different — meaning that his expression was different. She also noticed that he would laugh frequently without any apparent cause, contrary to his former way of doing. Sometimes he would laugh at whatever was said to him. She noticed, too, that he had difficulty in coughing and that he did not seem to be able to cough up the accumulations in his throat.

The patient complained of weakness in his hands and legs since Christmas of 1915, and noticed that when going downstairs his legs trembled and he felt insecure. He always staggered backwards when he lost his balance. He made no complaint of loss of sphincter control or of sexual disability.

His wife said that his memory was all right. She noticed that his neck gradually became larger and that, although formerly he had worn a size 15 collar with comfort, a number 16 now seemed rather tight for him. He did not complain of headache, and his appetite remained good and his bowels were regular. She stated that at times his speech was normal but that often it was necessary to ask a question several times and even to speak sharply before an answer was obtained. She also noticed that in friendly scuffles she was stronger than her husband, whereas formerly the reverse was true. His disposition, she said, was becoming ugly and he had attacks of violent temper which were quite short in duration. In one of these fits of anger he threw a piece of soap at her, striking her side and bruising it. Immediately after this he showed that he was sorry that he had hurt her.

Examination of Patient. — The patient was a very strong muscled, thick-set Italian. His face was expressionless and mask-like. (Figure 2.) Over the nose and each cheek, somewhat in the common distribution of lupus, there was distinct erythema, which whitened to finger pressure, and on the left cheek there was some scaliness. He closed his eyes, moved all his facial muscles, protruded his tongue in the middle line, and the tongue was not tremulous. He held his lips firmly under expiratory effort. He gave a short whistle but no longer whistled continuously as he had been in the habit of doing. He had difficulty, apparently, in taking a deep inspiration; repeated efforts failed of the desired result, and during the examination he seemed to be disturbed at times with an accumulation of mucus in his throat. Finger to nose test was accurate but irregularly tremulous. The patient stood well with his eyes closed, but not so well on his left foot as on his right. He walked in a rather uncertain fashion, though not in a definitely atypical way. Reflexes were normal throughout.

The patient signed his name and wrote his street number with comparative readiness, but his writing

FIG. 2. — (Case 1.) Showing the characteristic expressionless and mask-like facies.

was cramped and his wife said that it was different from what it used to be. His arterial pressure was 70–92, with a pulse of 80. His tremor was not much exaggerated on volition; he poured water from one test tube to another fairly well. There was no body tremor, no tremor at rest. He articulated every word but not clearly, and his speech was muffled and difficult to understand, seemingly because of the motionless condition of his lips and mouth parts in the effort of speech. At times during the interview

he did a little laughing without its being apropos, and at other times he laughed at something that was said which he may have considered amusing (Figure 3). Voluntary strength and grasp and resistive movements at the elbow and shoulder and in the

FIG. 3. — (Case 1.) Unmotive laughter was a prominent symptom in this case.

lower extremity seemed to be very great, in spite of his complaints of weakness.

During the examination the patient stepped off the scales backward and was unable to stop until he had walked backward to the opposite wall, a distance of about 12 feet. Then it was noted that if he were given a slight push in a backward direction he would walk back several steps before recovering his balance. He expressed no sense of fear of falling and smiled as he walked back.

While the patient was in the hospital for observation it was noted that he slept a great deal during the day as well as at night. His pulse, temperature and respirations were normal.

An X-ray examination failed to reveal any pathology in the lungs or gastro-intestinal tract. His urine was normal. His feces and urine were examined for traces of manganese, but none was found. A Wassermann test on the patient's blood gave a frank negative reaction. Blood examination showed hemoglobin 85 per cent., white cells 7,250, red count 5,640,000. As a probable explanation of this unusually high erythrocyte count, it should be understood that there was added to the ferro-manganese at intervals a certain amount of limestone and coke, and it is possible that there was a sufficient amount of carbon monoxide given off from this coke — there being no air supply to the interior of the furnace — to produce a mild form of carbon monoxide poisoning.

CASE 2. *History.* — S. K., a Hungarian, aged 32, a married man, without children, had been in the employment of the Steel Company since Feb. 17, 1906, but he was laid off on account of lack of employment on March 6, 1908, and he returned to work on Oct. 20, 1908. During this time he was employed as a runner in the converter until May 7, 1913, when he became a weigher at the electric furnace, weighing the manganese in the ladle as it was poured from the furnace. He was doing this work until the latter part of 1915, when he found that he was unable to continue. On Jan. 31, 1916, Mr. S., the superintendent of the Bessemer department, stated that this man had for some time past been a very able and efficient workman but that he had noticed a gradual decrease in his energy and mental acuteness, and had thought that he was becoming lazy. Mr. S. said that the man seemed to be dull mentally and that his movements were sluggish, and that when asked why his work was so poor he responded that he did not know, and seemed indifferent.

This patient was examined first on Feb. 1, 1916, and has been under observation at various times since. When questioned, he stated that he never had any serious illness, accidents, or dissipated habits. A little over a year before the first examination, he began to notice that he was having some difficulty in walking — a tendency to trot forward or backward when first starting off, and a little trouble in going down hill or downstairs. He had no feelings of dizziness, however. He said also that he had some numbness in his fingers and his toes. About this time his speech became muffled and indistinct. He became weak, and had continued so up to the time of examination.

Examination of Patient. — At the time of the first examination, the patient presented a peculiar facial

expression, a mask-like face (Figure 4), commonly with the contours and appearance of a fixed smile which showed his teeth. This was not invariable, but was frequently present and tended to be rather persistent. He walked fairly well, but said that he had

FIG. 4. — (Case 2.) This patient presented a peculiar facial expression, mask-like face, with the appearance of a slight, continual, fixed smile.

an inclination to hurry ahead and he did, as a matter of fact, walk with rather short, hastening steps. He also indicated that at times he ran backwards. He said that he slept well, had a good appetite, good digestion, good bowel action, entire control of the bladder, and a reasonable amount of sexual ability. He said that he had no sensory disturbance, but his hands were cold and cyanotic, and the nutrition of the cuticle about the nails did not seem to be good — that is, there was a suggestion of glossiness about the skin.

Cranial nerves seemed to be all normal as to voluntary control and as far as reflexes were concerned. The deep reflexes were also all present and about normal, certainly not at all exaggerated. This was true of heel jerks, knee jerks, wrist and elbow jerks.

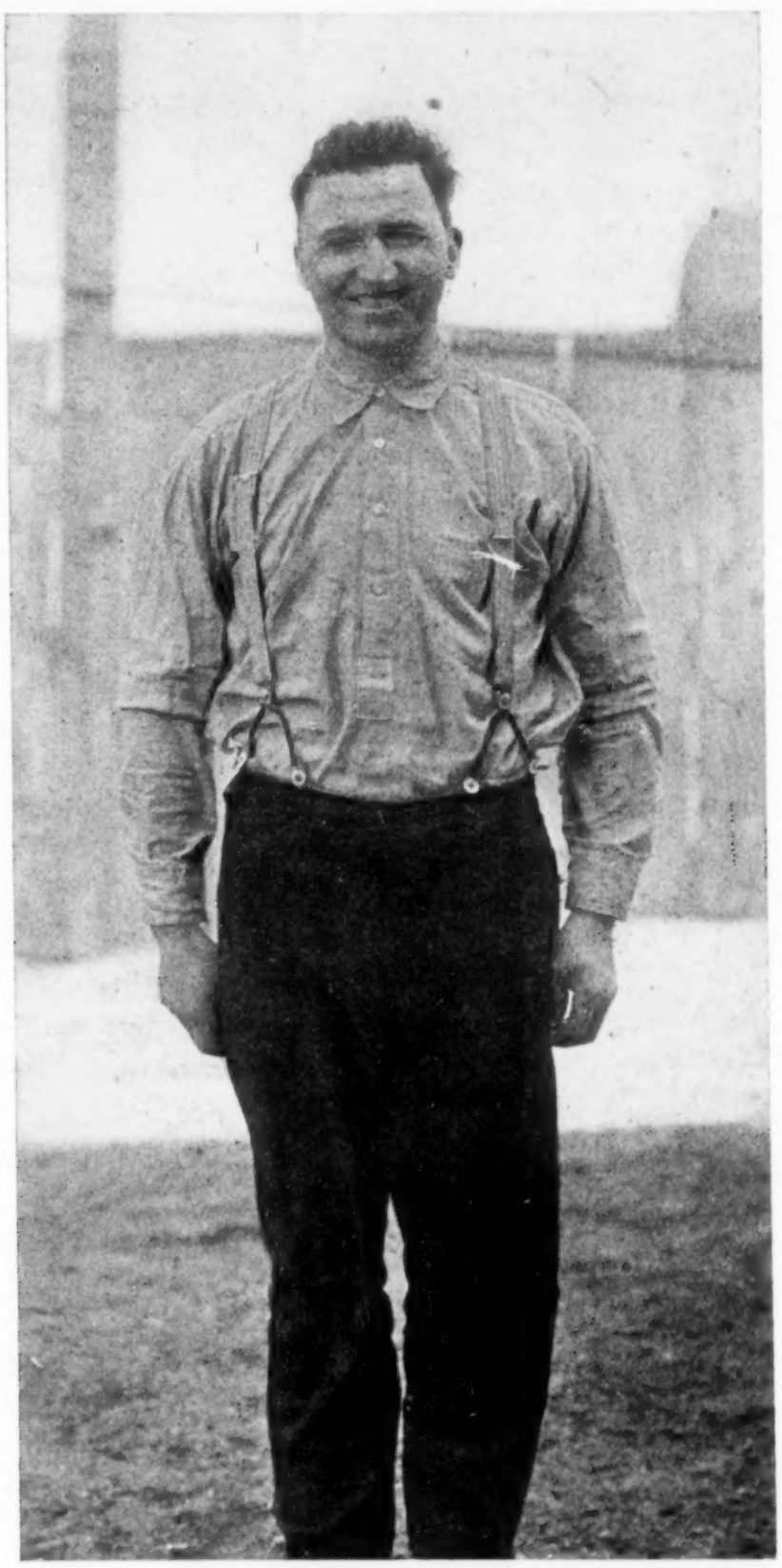

FIG. 5. — (Case 2.) Unmotive laughter was a prominent symptom in this case also.

The patient's writing was small and cramped and attempts to write a larger script even with a pencil failed. He wrote, however, with readiness and even with a fair amount of speed for a laboring man. He said that he could read and write but that he did not spend any time in reading. His speech was particularly peculiar. He talked with lips slightly retracted and motionless, teeth almost together, tongue apparently immobile, and his voice was low and monotonous, the enunciation deliberate and obscured. He tended to answer in monosyllables, and

seemed to have great difficulty in formulating a sentence. When asked how long he had worked on the furnace, he undertook to say that he had worked two years and eight months, and after a long pause one could understand the "two," and he drawled "aaaa" for a long time until it seemed that it would be impossible for him to enunciate anything at all, and at the end of a continuous drawling "a," dropped out "eight months" rather abruptly. It was impossible to understand him when he attempted to explain anything, and anything besides "yes" and "no" could be understood only with considerable uncertainty and guessing, yet he seemed mentally clear though apathetic.

No decided tremor was observable, but upon having the patient extend his fingers one could see and feel a tremulousness in the hands and arms, with some lack of co-ordinate control of the phalanges of the fingers. He poured water from one tube to another with steadiness and precision. He made all sorts of indicated voluntary movements with readiness. His grasp was greatly weakened in both hands, and his ability to resist passive movements communicated to his arms, especially at the elbows by the contraction of the biceps, was reduced. The leg muscles also seemed somewhat weakened. The eye grounds were normal.

Examination of the blood showed hemoglobin 90 per cent., leukocytes 8,000, erythrocytes 6,400,000. This unusually high red cell count was the result of a mild form of carbon monoxide poisoning, the explanation of which is noted in the preceding case. A Wassermann examination of the blood was negative. A chemical analysis of the urine and feces showed no trace of manganese. The urine examination was otherwise negative. An X-ray examination of the lungs showed no evidence of manganese infiltration. The patient's temperature, pulse and respirations were normal. A tendency to sleep and unmotive laughter were marked symptoms (Figure 5).

In May, 1917, it was noted that there was a marked falling out of the patient's hair, and on the right side along the hair line above and behind the right ear for a length of 5 inches, there was an area about 1 inch wide which was entirely denuded of hair. The hair in other parts of the scalp was easily removed by slight pulling.

The diagnosis of chronic manganese poisoning in these two cases was first made by Dr. Huey. The neurological examinations were later made by Dr. Archibald Church who confirmed the diagnosis.

The operation of the electric furnace, which was used to melt the manganese compounds, was discontinued when it was established that these men were suffering from chronic manganese poisoning. This was done because no practical way was found to eliminate entirely the dust and fumes from the furnace when it was in operation.

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TRINITROTOLUENE POISONING — ITS NATURE, DIAGNOSIS, AND PREVENTION *

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INTRODUCTION

WITH the entrance of the United States into the World War, the prevention of poisoning among American munition workers presented a public health problem of considerable importance. Previous experience in other countries had demonstrated that the productiveness of munition plants was dependent, to a large extent, on the prevention of such poisoning. Protection of the health of thousands of workers engaged in this industry was also a matter of much concern. Our allies, Great Britain in particular, had fortunately given this matter serious thought and considerable scientific work had been done with a view to reducing the health hazards in munition plants.

The most important explosives used for the manufacture of shells belong to the group of nitro derivatives of aromatic hydrocarbons, aniline and phenol. Among these nitro-compounds, trinitrotoluene (commonly called T.N.T., triton, or trotyl) was predominantly used in this country and in England on a very large scale. Inasmuch as the experience with this explosive in Great Britain had called attention to the serious health hazards connected with its manufacture, and especially its handling in the filling of high explosive shells, there appeared soon after the entry of the United States into the war several articles dealing with this subject.

In the Public Health Report of Nov. 16, 1917, Surgeon J. W. Schereschewsky (1), of the United States Public Health Service, gave an exposé of the practical aspects of the problem as ascertained by an inspection of the plants where T.N.T. was manufactured or used in the filling of shells. W. G. Hudson (2) (3), medical director of the Du Pont Company, and Alice Hamilton (4), of the United States Department of Labor, also contributed papers dealing with T.N.T. poisoning in factories in this country. H. S. Martland (5) described the first fatal case of T.N.T. poisoning which had occurred in the United States.

Although no accurate statistics were available on the incidence of T.N.T. poisoning in this country, inspection of various factories engaged in this industry had shown that the health of a considerable number of workers was affected by the constant contact with T.N.T. Being charged by Congress with the safeguarding of the health of the civil population, it became the duty of the United States Public Health Service to undertake an investigation of the best ways and means for the prevention of T.N.T. poisoning, inasmuch as it was evident that the available information was not adequate enough to lay down safe rules for this purpose. For instance, no satisfactory data were known as to the production and characteristics of T.N.T. poisoning in animals, data which were obviously needed to serve as a firm basis for the understanding of the nature, diagnosis, and prevention of T.N.T. poisoning in man. Accurate observations were also lacking in regard to the degree of contamination of factory air with T.N.T. under various conditions, data which are essential for purposes of proper ventilation of these plants. For these reasons the Hygienic Laboratory undertook a co-operative investigation, the Division of Chemistry concerning itself with (1) the

* The details and the methods used in this investigation will be found in Hygienic Laboratory Bulletin No. 126.

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determination of the vapor pressure of T.N.T. at various temperatures and the amount of T.N.T. present in the air of various parts of a shell-filling plant, and (2) the quantitative determination of T.N.T. or its derivatives in the urine. The Division of Pharmacology was charged with the study of the pharmacological aspects of the problem, with particular reference to (1) the elaboration of reliable and simple tests for the diagnosis of mild poisoning, (2) the investigation of the channels of absorption to the poison by the animal body, (3) the discovery of prophylactic methods, etc. It was in the nature of the problem that the practical aspects dealing with the recognition and prevention of T.N.T. poisoning should receive the major attention, although a number of very interesting observations were made which, as will be seen, have an important bearing on the subject of blood destruction and regeneration.

The data included in this report deal with the work done by the Division of Pharmacology. They are divided into two parts, the first one dealing with experimental T.N.T. poisoning as produced in dogs, and the second with the investigation of T.N.T. poisoning in a large shell-filling plant. The results obtained by the Division of Chemistry will be published elsewhere.

Experimental T.N.T. Poisoning in Animals

As previously stated, the literature contains little satisfactory information concerning the production of typical T.N.T. poisoning in animals. White and Hay (6), on the basis of a few experiments on cats and rabbits, considered T.N.T. "as not poisonous under ordinary use." Moore, Webster, and Wyon (7) state that they were not successful in producing toxic symptoms in guinea-pigs exposed for several weeks to T.N.T. fumes in factories, whereas kittens under similar conditions showed evidence of poisoning (cyanosis). The animal work of these investigators was largely confined to rabbits and guinea-pigs, which were given one or a few large doses, ranging from 10 to 9,000 mg. per kilo body weight. The British report, while containing extremely valuable information, does not include any really satisfactory information on T.N.T. poisoning in animals. This is due to the fact that the species of animals selected for the work happened to be highly resistant to the toxic action of T.N.T. It is, of course, possible to kill even a highly resistant animal with massive doses of the poison, but it is questionable as to whether the symptoms and pathological changes thus produced correspond to those found in T.N.T. workers who, according to clinical observers, must be exposed to T.N.T. for at least four weeks.

During the progress of our work a brief abstract of the work of Kramer and Meierhof (8) appeared, in which these authors reported some experiments dealing with T.N.T. poison in dogs. They noted the following symptoms: vomiting, diarrhea, depression, and weakness. Examination of the blood revealed the presence of a leukocytosis, polychromasia, and an increase in nucleated red blood cells. The necropsy findings were negative, with the exception of a moderate degree of central degeneration in the liver and an increase of blood pigment in the bone marrow, lymph nodes, and spleen. They called attention to the absence of any lesions which might explain the death of the animals, particularly the absence of acute yellow atrophy of the liver.

It was therefore necessary to find a highly susceptible animal.

General Plan of Investigation

Preliminary experiments with guinea-pigs and albino rats confirmed the previously noted statements of the British

investigators that these animals are highly resistant to T.N.T. That the animals absorbed the poison was evident from the change in the color of the urine and the positive Webster test. In rats the urine contains a bright pink pigment after T.N.T. is given either by mouth or subcutaneously. The first few experiments with dogs and cats, however, showed that these animals develop the typical symptoms which are seen in T.N.T poisoning in man. Dogs were finally chosen for this investigation as these animals seemed to be sensitive to T.N.T. and as they were of sufficiently large size to permit the frequent withdrawal of small quantities of blood for examination.

In view of the fact that T.N.T. poisoning in munition workers is essentially of a chronic nature requiring several weeks or even months for its full development, it was desirable to produce an analogous condition in dogs by the repeated administration of relatively small doses of T.N.T. over a long period of time. A small number of experiments dealt with a study of acute poisoning. For this purpose a single large dose (100 mg. per kilo) of the poison was given.

For the production of chronic poisoning the doses ranged from 5 to 33 mg. per kilo body weight given every day except on Sundays and holidays. The T.N.T. used in this investigation was obtained from various shell-filling plants and represented a product of average purity. A chemically pure T.N.T. was prepared for us by Dr. Marcus of this laboratory. In most of the experiments the poison was administered either by mouth in the form of gelatin capsules or subcutaneously dissolved in olive oil. A small number of animals received the T.N.T. in the form of fine dust directly into the lower air passages. For this purpose the animals were anesthetized. A small catheter was inserted through the trachea into the left bronchus and the fine T.N.T. dust was then blown into the lungs, this being followed by the immediate withdrawal of the catheter, care being taken that none of the poison should come into contact with the animal's mouth. A few animals received the poison dissolved in oil intraperitoneally.

The condition of the animals was carefully watched and the kind and severity of symptoms observed were recorded daily. A specimen of urine was secured each day (except Sundays) by means of catheterization, and these urines were submitted to various tests for the presence of abnormal constituents, such as sugar, protein, bile pigment, and T.N.T. and its derivatives.

Particular attention was also paid to changes in the blood in this condition. For this purpose the blood of each animal was carefully examined prior to and following the administration of the poison. In a considerable number of the animals a complete blood study was made, including a quantitative estimation of the hemoglobin, the total blood volume, plasma volume, and pigment volume, the number and character of the red cells, a leukocyte and differential count, the number of reticulated and nucleated red cells, the coagulation time of the blood, and the presence or absence of bile pigments and T.N.T. derivatives in the serum.

In view of the fact that the work of Hunt (9), of Opie and Alford (10), and of Salant and Swanson (11) had shown that the character of the diet has a marked influence on the toxicity of various substances, and as Hooper and Whipple (12) had demonstrated that blood regeneration is materially influenced by the composition of the diet, it seemed important to study the effect of various diets on the course of the T.N.T. poisoning. Three diets were chosen for this purpose: (1) a bread and milk diet, composed of approximately equal parts per weight of pasteurized milk and white bread; (2) a meat diet, consisting of medium fat beef with or without the

addition of calcium phosphate; and (3) a mixed diet containing white bread, pasteurized milk, and medium fat beef in the proportion of 3, 3 to 1. The relative proportions of protein, fat, and carbohydrates in these three diets were as follows:

	Protein	Fat	Carbohydrate
Bread and milk	15	7	78
Mixed.....	20	14	66
Meat.....	45	65	0

These figures show that the bread and milk diet is rich in carbohydrates and relatively poor in fats and proteins. The meat diet, on the other hand, is rich in fat and protein, and the mixed diet occupies an intermediate position.

Inasmuch as the British report had called attention to the probable conversion of T.N.T. within the body into certain reduced compounds, particularly a hydroxylamine derivative, a number of reduction and oxidation products of T.N.T. were prepared, and their pharmacological action compared with that of T.N.T. The solubility of these compounds in oil and water was also determined. This phase of the work is of interest with respect to its bearing on the fate of T.N.T. in the body and the mechanism of the toxic action of the substance on the tissues and particularly the red blood corpuscles. A careful necropsy was made on all animals which died and all the tissues, with the exception of the central nervous system, were subjected to histological examination.

Explanation of Charts. — The charts and their legends contain the essential information relating to and the results obtained by the experiments. The number and time of administration of the doses of T.N.T. are indicated by the arrows at the bottom of the charts. The figures immediately above represent the number of nucleated red cells per 200 white cells counted. The curves were obtained by plotting the initial value obtained before the animal received T.N.T. as 100 per cent. The curves therefore represent the percentage fluctuations and give a clear picture of the course of the poisoning as determined by the body weight and the blood changes.

Discussion

(*a*) *Symptomatology.* — In munition workers various symptoms, such as dermatitis, gastro-intestinal pain, constipation, bleeding from the nose, giddiness, cyanosis, breathlessness after slight exertion, anemia, and jaundice, have been attributed to the toxic action of T.N.T. The symptom-complex varies with the individual. In the milder form of poisoning, which is spoken of as "minor T.N.T. sickness," there may be present cyanosis, dermatitis, nose bleeding, constipation and giddiness. The severer forms of poisoning have been divided into toxic jaundice and aplastic anemia.

Doses of T.N.T. ranging from 5 mg. to 100 mg. per kilo body weight produced a more or less severe grade of intoxication, the severity of the latter being somewhat dependent on the size of the dose. After the larger doses the animals showed marked symptoms within a few hours, whereas the lowest dose used (5 mg. per kilo) did not always lead to recognizable clinical manifestations.

The striking feature of T.N.T. poisoning in dogs is the fact that *individual susceptibility* plays a very important part. Certain animals receiving a fairly large dose may not show as marked symptoms as others receiving 50 to 75 per cent. less T.N.T. This difference in individual susceptibility is very probably not due to differences in the rate of absorption of the poison, as T.N.T. is absorbed fairly rapidly. It is more likely that different individuals deal differently with the poison after the poison is absorbed, a point which will be dealt with later on.

Most of the animals developed within the first day after the administration of the T.N.T. a very pronounced *cyanosis*, a

symptom which is very common in T.N.T. workers. The mucous membrane and tongue of the dogs assumed a dark purplish color. This cyanosis was observed in some dogs as early as four hours after the administration of a fairly large dose. In a few animals which had received one large dose or repeated small doses this symptom was entirely lacking, in spite of the fact that these animals finally died from the effects of the poison. In animals receiving the poison over a long period of time the cyanosis usually cleared up after the first two weeks, giving place to an anemic appearance of the mucous membranes. At its height the cyanosis may be associated with a marked dyspnea, and the blood always contains considerable methemoglobin and is chocolate-brown in color. Oxygen inhalation has no effect whatever on the cyanosis, a fact which proves that the latter is essentially due to the large amounts of methemoglobin of the blood.* It is, however, possible to lower the increased pulse rate and respiration observed in this condition by allowing the animal to breathe a mixture of air and oxygen.

In some of the experiments a very marked *incoordination* was noted, which first appeared on the second or third day. When this occurs, the animal staggers and is apt to fall when attempting to walk downstairs. The incoordination is usually associated with a marked cyanosis and disappears in the later stages in chronic poisoning. It appears as if this symptom is due to a temporary functional abnormality of the cerebellar centers.

Vomiting and *salivation* were observed in a number of animals during the stage of acute intoxication. *Constipation* was sometimes noted, though as a rule the animals suffered from *diarrhea*. The *body weight* and nutrition were maintained in a satisfactory manner in a considerable number of experiments of long duration.

All animals developed an *anemia*, the principal features of which, and its causation, will be discussed separately. In six dogs a *marked icterus* was observed, this being preceded by the excretion of a considerable amount of bile pigment with the urine. Dermatitis occurs in T.N.T. workers, but was never observed in these animals. Ulceration of the mucous membrane, which was observed in the dogs on a bread and milk diet, has no relation to T.N.T. poisoning, but is due to a dietary defect.

(*b*) *Paths of Absorption of T.N.T.* — From a practical point of view it was important to determine by what channels T.N.T. can gain access to the blood and tissues. Under the conditions prevailing in the factories, the T.N.T. workers may come into contact with both T.N.T. vapor and dust, thus exposing the skin and the respiratory and gastro-intestinal tracts to the poison. It was, therefore, necessary to determine whether these organs absorbed T.N.T.

Experiments which are not reported in detail have shown that dogs and cats which had received T.N.T. dust directly into the lower air passages developed a marked cyanosis within twelve hours, and their urine revealed the presence of a T.N.T. derivative. T.N.T. is evidently very readily absorbed by the epithelial cells of the bronchi. On account of the probability of producing a pneumonia by this method of administration, no attempts were made to cause chronic poisoning in this way.

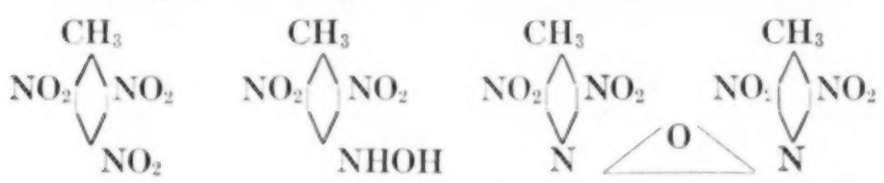
T.N.T. is also very readily absorbed from the gastro-intestinal tract when it is given in the form of gelatin capsules. As T.N.T. is very readily soluble in fat, it might be expected that fat would favor its absorption. The comparison of the results obtained in animals fed either on a diet

* This methemoglobin formation is due to the reduction of T.N.T. to a hydroxylamine derivative, the latter acting on the hemoglobin. Letsche (13) in *Ztschr. f. physiol. Chem.*, 1912, Vol. 80, p. 419, has shown that hydroxylamine converts oxyhemoglobin completely into methemoglobin.

poor in fat (bread and milk) or on a fat-rich diet (fat meat), however, shows that the presence of a considerable amount of fat in the food does not favor the absorption in any way. Within six hours after the feeding of T.N.T., the urine yields a positive test for the presence of a T.N.T. derivative (Webster test), and cyanosis, incoordination and dyspnea are observed.

The poison is also absorbed with great ease when injected subcutaneously in the form of a 3 per cent. solution in olive oil. These injections, even when repeated daily over several weeks, do not seem to lead to any local irritation at the site of injection. Kramer and Meierhof (8) state that they have been able to produce T.N.T. poisoning in dogs with great regularity by means of skin inunction. We have not used this method, principally on account of the impossibility of ascertaining the amount of T.N.T. actually absorbed. T.N.T. is also readily absorbed from the peritoneal cavity. In conclusion, it is safe to say that T.N.T. is readily absorbed from the respiratory and gastro-intestinal tracts, the subcutaneous tissue, the peritoneal cavity, and the intact skin.

(*c*) *Fate of T.N.T. in Body.* — Moore and his associates of the British Medical Research Committee (7) briefly state in their report that T.N.T. is reduced, within the animal body, to 2, 6-dinitro-4-hydroxylaminotoluene, which is readily converted into 2, 6-dinitro-4-azoxytoluene. The chemical relation of these three compounds is brought out by the following formulae:



The hydroxylamine derivative is then conjugated with glycuronic acid and excreted in this form in the urine. Although the announced paper on this subject has not appeared up to this date,* it seemed of considerable interest to consider this question of the fate of T.N.T. From previous work on the metabolism products of toluene and aromatic nitro-compounds, it is *a priori* possible that both oxidation and reduction might play a rôle in the modification of T.N.T. According to Nencki and Giacosa (14) toluene is oxidized in the body to benzoic acid. Jaffe (15) isolated from the urine of dogs which had received large doses of paranitrotoluene a substance which he identified as paranitrobenzoic acid, part of which was conjugated with glycocoll to nitrohippuric acid. Meyer (16) was able to isolate paraaminophenol from the urine of a case of nitrobenzene poisoning. He also confirms some older observations of Lewin (17), who claims that azoxybenzene occurs in the urine of animals poisoned with phenylhydroxylamine. Walko (18) reports experiments which indicate that picric acid is reduced in the body to picramic acid.

That trinitrotoluene does not occur as such in the urine of T.N.T. workers was shown by Moore and confirmed by us in the case of the urine of dogs poisoned with T.N.T. The so-called Webster test, which is used for this purpose, is based on the fact that an ethereal solution of T.N.T. assumes a purplish-red color after the addition of an alcoholic solution of potassium hydroxide. This test is always negative in the dog's urine if the fresh urine is directly extracted with ether. According to Webster it is essential to acidify the urine with 20 per cent. sulphuric acid before the ether extraction. The ether extract so obtained then yields a dark purplish-red color upon the addition of an alcoholic potash solution. When carried out in this latter way, the test is usually positive in the extract obtained from the urine of dogs which have received T.N.T., indicating that unchanged T.N.T. is absent, but that a derivative giving the same test is present. This derivative, according to Moore, is the above-

* See British Medical Research Council, Special Report Series, No. 58, 1921.

mentioned hydroxylamine compound which has to be split off from its combination with gyleuronic acid by the acid treatment. We found that the only derivative of T.N.T. which yields the same color as T.N.T. itself is the hydroxylamine compound. It is, therefore, very probable that the hydroxylamine compound is one of the metabolism products of T.N.T. We have repeatedly examined the feces of our animals for the presence of T.N.T., but have never been able to get a positive Webster test. The bile, however, very often yields positive tests. Here also, as in the case of urine, it is necessary to add acid before carrying out the ether extraction, a fact which indicates that T.N.T. as such is not present and that, therefore, the test is probably due to the hydroxylamine derivative.

As to the quantity of the hydroxylamine compound which is excreted with the urine very little can be said, except that the method described by Elvove (19) when applied to dog's urine accounts for only from 9 to 42 per cent. of the T.N.T. given to the animals.

An important fact which we wish to emphasize particularly is the absence of any relation between the urinary Webster test and the severity of the intoxication, as determined by the clinical symptoms and the grade of the anemia. The data presented in this report conclusively show that the Webster test may be persistently negative in spite of the presence of marked cyanosis and incoordination, and that, on the other hand, it may be strongly positive in animals in which the symptoms are not especially pronounced.

We have also frequently made the observation that during the first month of chronic poisoning the urine of the dog yields a very marked Webster test, but that this test nearly always becomes negative in the later stages of poisoning, and this in spite of the fact that the animal still receives the poison and shows evidence of a progressing anemia. We believe that this is an indication of a change in the disposition of the poison by the body, in the sense that the hydroxylamine compound is further reduced to the mono or diamino derivative of T.N.T., substances which do not give the Webster test but which possess the same pharmacological action as T.N.T.

It is also possible that part of the T.N.T. is oxidized to trinitrobenzoic acid, which would combine with glycocoll to form trinitrohippuric acid. We have been able to show that trinitrobenzoic acid, when given in doses of the same order as those required for the production of T.N.T. poisoning, has no evident effect on dogs. This substance is, to say the least, much less toxic than either T.N.T. or its reduction products. This difference in toxicity of T.N.T. and trinitrobenzoic acid is very likely due to the greater water solubility of the latter, a fact which favors its rapid removal from the body through the kidney. It is quite possible that the difference in the resistance of different individuals to T.N.T. poisoning may be explained by assuming that the more resistant animals oxidize the methyl group of T.N.T. more readily than the more susceptible individuals.

There remains much to be learned about the fate of T.N.T. and other aromatic nitro derivatives in the body. May it suffice here to state that the marked variation in the resistance to the poison may be easily explained on the basis of the assumption that the reactions involved in the transformation of T.N.T. in the body may differ both qualitatively and quantitatively in different animals of the same and different species.

Trinitrotoluene or some of its derivatives are retained in the tissues for a considerable time, as shown by the progressive anemia observed in dogs after a single dose of the poison and the slow recovery after the animal is taken off T.N.T. This retention of T.N.T. or its reduction products is

probably due to the fact that these compounds are very insoluble in water, rendering their elimination with the urine difficult.

(*d*) *Necropsy Findings.* — All of the animals that died from chronic T.N.T. poisoning were anemic and showed the following characteristic pathological changes which must be attributed to the action of this poison:

The endothelial phagocytes of the spleen pulp, bone marrow, and liver contained engulfed red cells and a varying amount of granular hemosiderin. These pigment granules were frequently as large as red corpuscles. The pigmentation was most striking in the spleen and bone marrow. (Fig. 1.) The liver pigment was usually confined to the swollen Kupffer cells within the liver capillaries. At times groups of hemosiderin-containing phagocytes were found about the portal spaces. The liver cells rarely contained even a small amount

FIG. 1. — Spleen pulp in chronic poisoning containing maximum amount of hemosiderin. Perl's reaction.

of finely granular hemosiderin. (Fig. 2.) The mesenteric lymph glands occasionally contained a few hemosiderin-holding phagocytes.

A mild icterus was found in six of the thirty-nine animals. In these cases the subcutaneous fat and the intima of the aorta yielded a positive test for bile pigment.

A myeline degeneration of the sciatic nerve occurred in the majority of the ani-

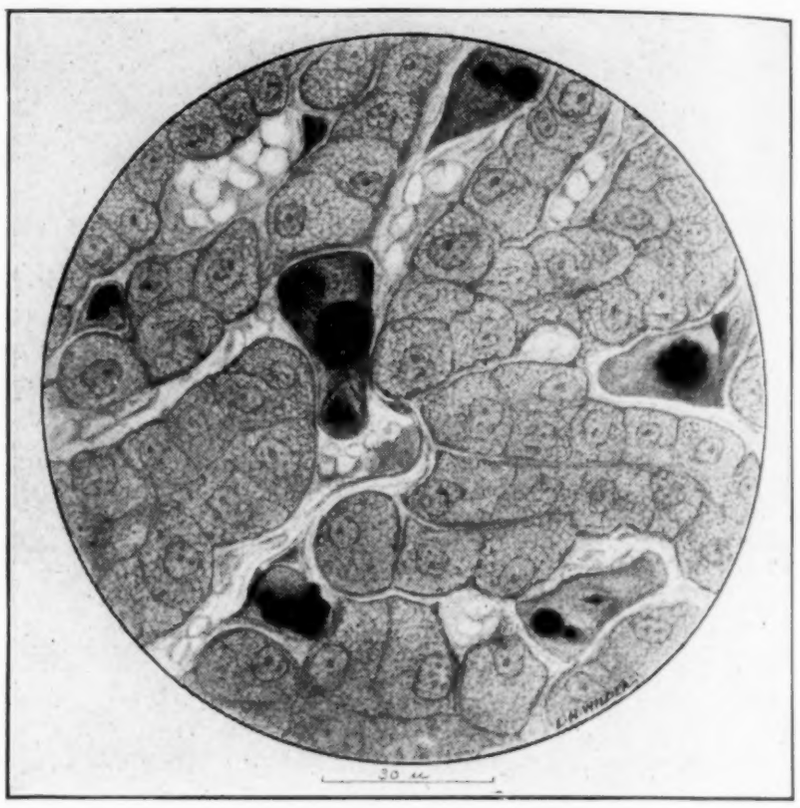


FIG. 2. — Liver in chronic poisoning showing the hemosiderin in the swollen Kupffer cells within the liver capillaries. The liver cells do not contain hemosiderin. Perl's reaction.

mals in which this nerve was examined histologically, irrespective of diet.

In some of the dogs fed on medium fat beef the liver showed a definite fatty change chiefly confined to the liver cells surrounding the efferent veins. Hyaline necrosis was not found, although in a few cases small areas of focal necrosis were detected.

Animals sacrificed within a few days after administration of relatively large doses of T.N.T. showed a varying degree of splenic tumor. In these animals the endothelial phagocytes of the spleen pulp, bone marrow, and the Kupffer cells of the liver contained many engulfed red corpuscles, apparently intact, and a small amount of granular hemosiderin. (See Figs. 3, 4, 5.)

A hyperplastic bone marrow was found in all of the animals except those sacrificed within a few days after the administration of the first dose.

In addition to the above changes a number of the animals with a complicating in-

tercurrent infection showed bronchopneumonia, acute nephritis, cloudy swelling of the liver, and splenic tumor. Two dogs of the mixed diet series and five dogs of the

FIG. 3. — Mononuclear phagocytes with engulfed red cells from the spleen pulp in acute poisoning.

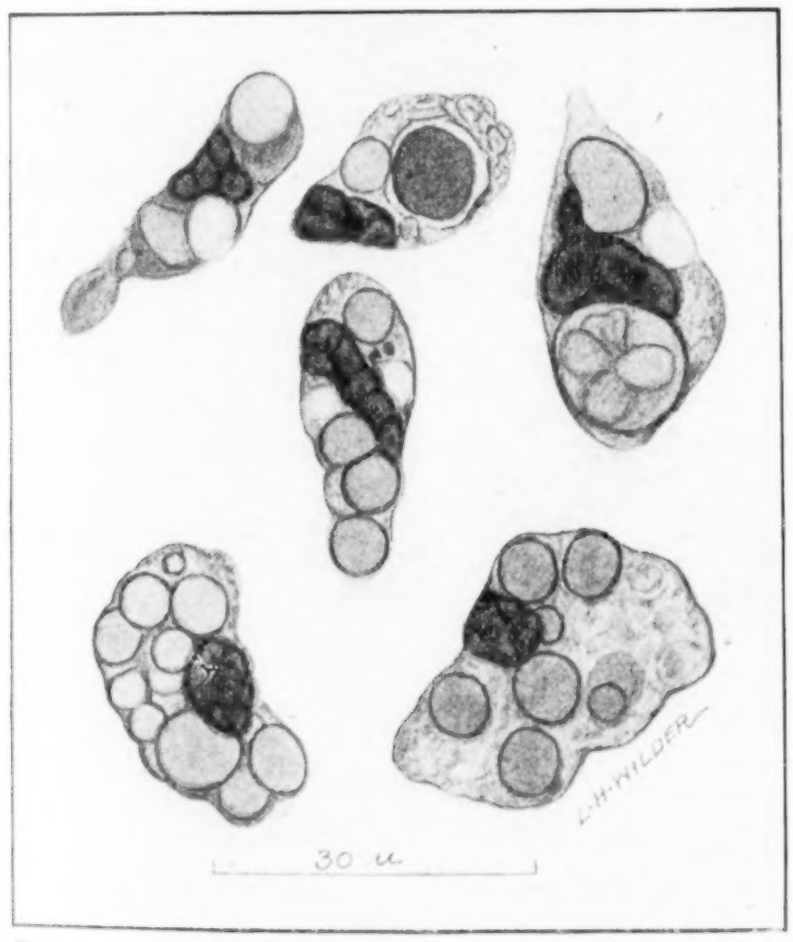


FIG. 4. — Kupffer cells containing red cells and pigment from the liver capillaries in acute poisoning.

bread and milk diet series showed an extensive superficial ulceration of the oral mucous membrane, changes brought about by the deficient diet and not by T.N.T.

(*e*) *Pathogenesis of Anemia and Icterus.* — The salient feature of chronic T.N.T. poisoning in dogs is the anemia so constantly present and the mechanism of this red cell destruction. On reviewing the literature on physiological blood destruction it is evident that a certain proportion of the erythrocytes are continuously broken down and replaced. Ashby (20) showed that the length of life of transfused blood corpuscles in man is thirty days and more. As to the fate of the erythrocytes, present knowledge is still inadequate.

As long ago as 1901, Hunter stated that two different processes of blood destruction

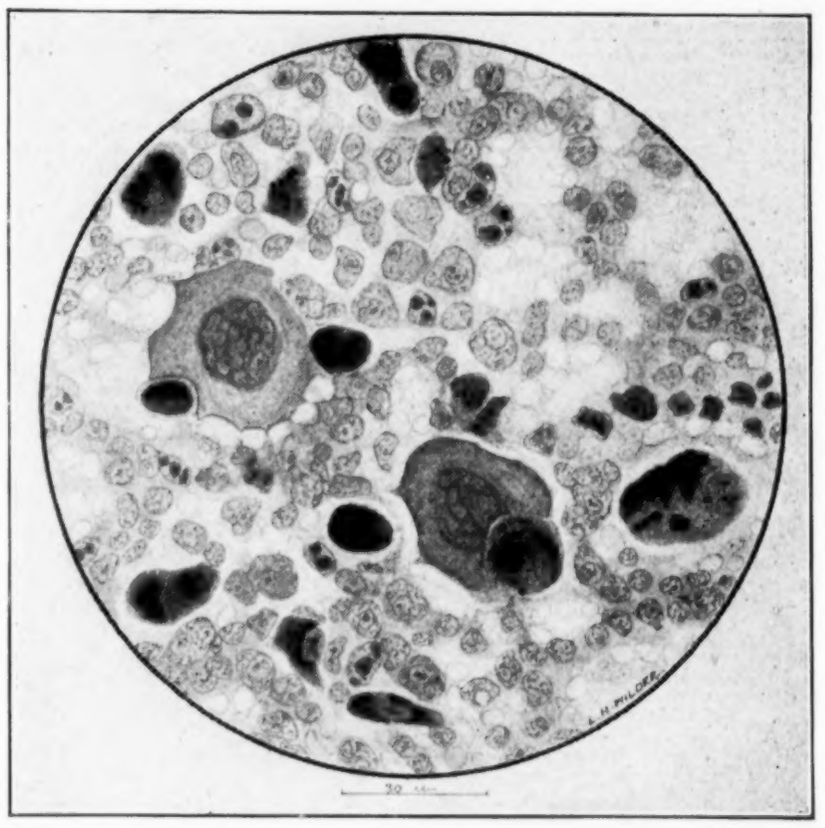


FIG. 5. — Bone marrow in chronic poisoning. Note the amount of hemosiderin within the phagocytic cells. Perl's reaction.

may be distinguished — one in which the red corpuscles are phagocytosed without loss of hemoglobin, the other in which the red corpuscles undergo hemolysis with the liberation of hemoglobin within the blood stream. The first process is characterized by a gradual decay of the red corpuscles while still circulating. They become spherical, deeper in color, and retain their hemoglobin until they are enclosed within the active cells of the spleen, or leukocytes of the blood, and are stored up within the spleen or in the capillaries of the liver. Within these cells the whole of the hemoglobin of the corpuscle is converted into

hemosiderin. The pigment so formed is characterized generally by the varying size of its granules, some of which correspond in size to that of the original red corpuscles. In the liver, the pigment is found within the capillaries and never within the liver cells. The second process is marked by the liberation of hemoglobin from the red cell within the blood stream. The hemoglobin escapes from the corpuscle, either alone or in combination with the albuminous stroma. It is carried to the liver and is broken up by the liver cells.

Recently Rous and Robertson (21) showed that a hemolytic process, in the ordinary sense of the term, at most plays a very minor part in normal blood destruction. They state that phagocytosis will not suffice as a general explanation of normal blood destruction and that the red corpuscles, in those species in which phagocytosis is negligible, are fragmented one by one, while still circulating, to a fine hemoglobin-containing dust which is eventually removed from the blood by the spleen, and under exceptional conditions by the bone marrow.

In certain anemias, on the other hand, such as those produced by hemolytic immune serum and by certain poisonous substances (toluylenediamine, sodium oleate, phenylhydrazine, arseniated hydrogen, etc.), the destruction of the red corpuscles takes place by hemolysis within the circulating blood. The hemoglobin escapes from the corpuscles into the plasma and a hemoglobinemia ensues. If the concentration of hemoglobin in the plasma is great enough, it will escape through the kidneys into the urine. The liver cells contain an excess of hemosiderin in consequence of hemolysis, not of phagocytosis of red cells. The hemosiderin granules so arising are small and more or less uniform in size.

According to Pearce, Austin, and Eisenbrey (22), hemoglobin escapes into the urine of normal dogs when the concentration of free hemoglobin in the blood plasma is approximately 0.06 gm. of hemoglobin per kilo of body weight. The blood of the dog contains approximately 16 per cent. of hemoglobin, so that it would require the hemolysis of the red corpuscles contained in only 4 c.c. to cause a hemoglobinemia in an animal weighing 10 kilos.

The anemia produced in dogs by T.N.T. is characterized by a very rapid destruction of the red corpuscles. The percentage of hemoglobin in the unit of blood diminishes. The pigment volume, representing the total amount of hemoglobin in the circulating blood at the time of the blood volume determinations, drops in certain animals to 50 per cent. or less within fifteen days, especially in those on a bread and milk diet. Coinciding with this decrease in pigment volume there is a marked diminution in the total blood volume corresponding roughly to the extent of the reduction of the red blood cell volume. This rapid blood destruction is not accompanied by the appearance of hemoglobin in the blood plasma or urine. In many cases there is also a complete absence of bile pigment in the blood plasma and urine. The number of red corpuscles is usually markedly decreased. In a few cases, however, the erythrocytes have fragmented to such a degree that their actual number per cubic millimeter of blood is considerably increased above normal, while the total pigment volume and red blood cell volume show a very marked decrease. (See Fig. 6.) Fragmentation of red cells has been most marked in dogs on a bread and milk diet. Anisocytosis, poikilocytosis, and polychromatophilia were common findings, the degree of such abnormalities usually corresponding to the degree of the anemia. The detailed examination for disintegrating red corpuscles in dogs acutely poisoned revealed the presence of considerable numbers of these cells in the blood, spleen, bone marrow, and liver. They were often small.

Sometimes they were as large as and even larger than the normal red cell. Most of them were characterized by a translucent blister-like elevation extending from a portion of the cell and having at times a somewhat irregular outline. The hemoglobin mass within these cells stained uniformly and deeper than the surrounding

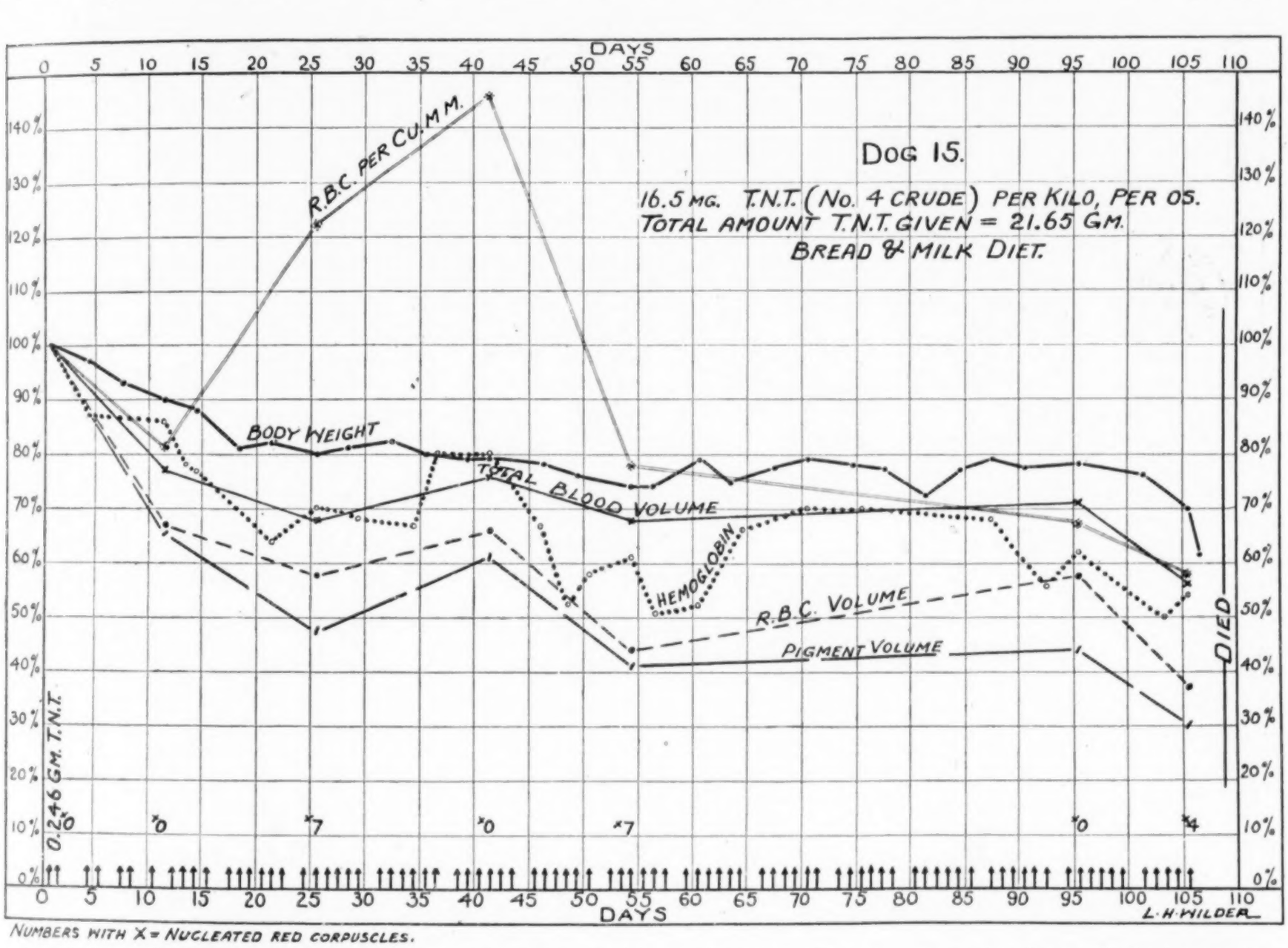

DAYS
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110
140% 130% 120% 110% 100% 90% 80% 70% 60% 50% 40% 30% 20% 10% 0%
DOG 15.
16.5 MG. T.N.T. (No. 4 CRUDE) PER KILO, PER OS.
TOTAL AMOUNT T.N.T. GIVEN = 21.65 GM.
BREAD & MILK DIET.
R.B.C. PER CU. MM.
BODY WEIGHT
TOTAL BLOOD VOLUME
HEMOGLOBIN
R.B.C. VOLUME
PIGMENT VOLUME
DIED
0.246 GM. T.N.T.
×0 ×0 ×7 ×0 ×7 ×0 ×4
L. H. WILDER
NUMBERS WITH X = NUCLEATED RED CORPUSCLES.

FIG. 6. — Adult male. Slight cyanosis, salivation, and incoordination. Food consumption fair. Slight icterus of conjunctivae between the 46th and 65th days and between 88th and 93d days, accompanied by an increase in bile pigments in the urine. Leukocytes varied between 4,200 and 22,400. Reticulated cells 12 to 95 during the first 71 days. Nucleated reds from none to 7. Anisocytosis and basophilia.

Autopsy. — Emaciation. Extensive superficial ulceration of oral mucous membranes. Bone marrow hyperplastic. Spleen pulp, liver capillaries, bone marrow, and mesenteric lymph glands contain hemosiderin-holding phagocytes.

Note the increased fragmentation of erythrocytes between the 12th and 54th days.

red corpuscles. Other cells were found in which the hemoglobin was apparently divided by a clear portion. (See Fig. 7.) Hemolyzing red corpuscles or red corpuscle shadows were not encountered.

Blood, aspirated from the external jugular vein within a few hours from animals given a moderate dose of T.N.T., is chocolate-brown in color and contains large amounts of methemoglobin on spectroscopic examination. The methemoglobin is confined exclusively within the red corpuscles and does not occur in the plasma.

As stated above, in the necropsy findings, the spleen pulp, bone marrow, and, at times, the mesenteric lymph glands contain numerous large mononuclear phagocytes loaded with granular hemosiderin — some of the granules are as large as the red corpuscles — and in acute poisoning, especially, the phagocytes contain engulfed red corpuscles. The Kupffer cells of the liver are swollen and contain hemosiderin and red corpuscles. At times there are groups of hemosiderin-containing phagocytes about the portal areas. The liver cells rarely contain hemosiderin.

A further important observation in determining the mechanism of the blood destruction is that T.N.T. does not produce hemolysis *in vitro* when added directly, or dissolved in olive oil, to defibrinated blood, citrated blood, or washed red corpuscles. From these experiments it is evident, however, that T.N.T. is absorbed by the red corpuscles, since part of the

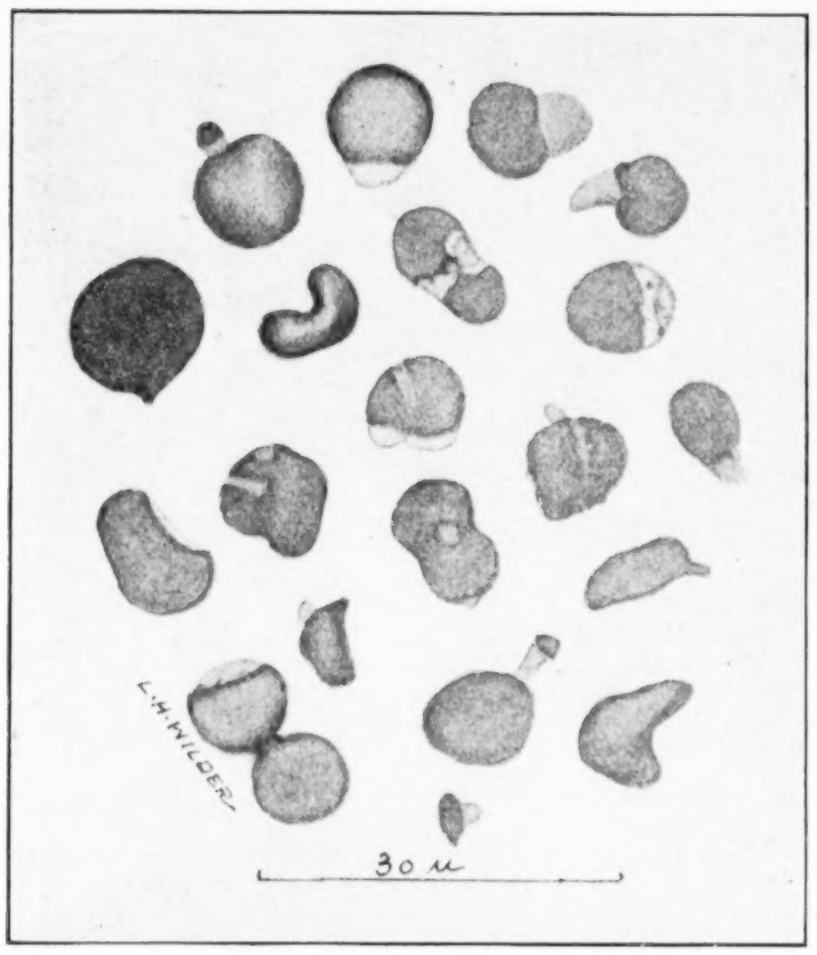


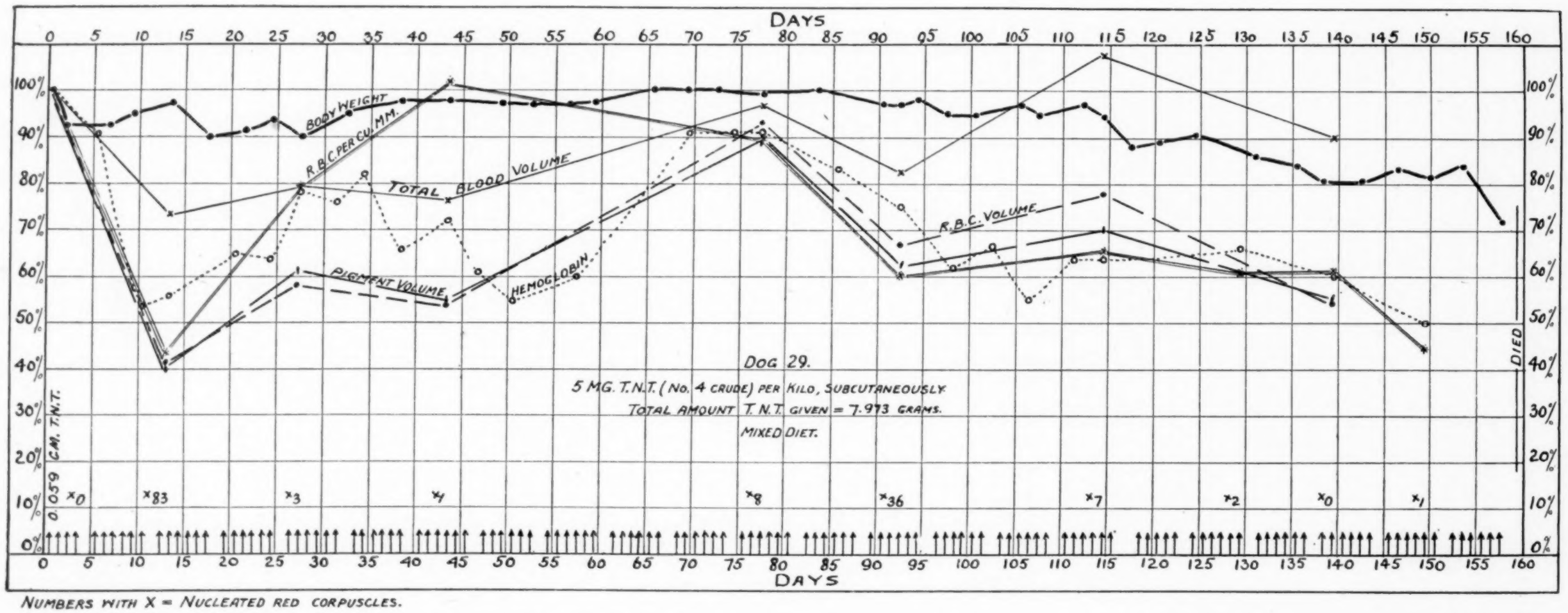
FIG. 7. — Disintegrating red corpuscles from the blood of an acutely poisoned T.N.T. dog. Wright's stain.

oxyhemoglobin is changed into methemoglobin within twenty minutes at 37° C.

On the basis of these observations the following explanation may be made of the mechanism responsible for the blood destruction in T.N.T. poisoning. *T.N.T. or some of its derivatives, being lipoid soluble, are absorbed by the red corpuscles and change part of the oxyhemoglobin into methemoglobin. Disintegration of the red corpuscles follows without the liberation of hemoglobin or methemoglobin into the blood plasma. The injured cells are then engulfed by the endothelial phagocytes of the spleen, of the bone marrow, of the lymph glands, to a certain extent, and by the endothelial Kupffer cells of the liver. The engulfed red cells are in turn broken down within the endothelial phagocytes with the formation of bile pigment and hemosiderin.*

The bile pigment which at times occurs in the urine of dogs poisoned with T.N.T. without the appearance of icterus can be easily explained when it is remembered that the dog's kidney excretes bile pigment very readily and that normally the blood plasma does not contain any bile pigment. A trace of bile pigment in the urine of normal dogs is commonly found, especially when the animals are constipated or during fasting periods. On the other hand, the threshold value of the human kidney for bile pigment is relatively high and plasma contains a considerable amount of bile pigment before it appears in the urine. Gilbert and Herscher (23) showed that the normal human serum contains from 25 to 35 mg. of bilirubin per liter. Panton (24) studied the blood of 100 munition workers exposed to T.N.T. and found that 20 per cent. had an increase of bile pigment in the serum without its appearance in the urine. The increase of bile pigment found at times in the urine of poisoned dogs corresponds to the increase of bile pigment in the plasma of munition workers — probably brought about in either case by the increased destruction of red corpuscles by the endothelial phagocytes and the consequent formation of bile pigment within these phagocytes.

Six dogs out of thirty-nine showed slight but definite clinical *icterus* of the mucous membrane of the mouth and conjunctiva, accompanied by the appearance of bile pigment in the blood plasma and considerable amounts in the urine. In four of these dogs the icterus appeared several days before death. At necropsy the intima of the aorta and the subcutaneous fat were definitely bile stained and gave positive tests for bile pigment. The kidneys in two of the animals were normal. The slight fatty changes occasionally found in the liver can-



NUMBERS WITH X = NUCLEATED RED CORPUSCLES.

FIG. 8. — Young adult female. Intermittent cyanosis, inco-ordination, and salivation during first part of experiment. No icterus. Food consumption good. Leukocytes 9,000 to 20,600. Reticulated reds 1 to 91 during the first 44 days. Nucleated reds none to 83. Anisocytosis, poikilocytosis, and basophilia.

Autopsy. — Oral mucous membrane shows a few superficial ulcerations. Bone marrow hyperplastic. Bone marrow, liver capillaries, and spleen pulp contain numerous phagocytes loaded with coarsely granular hemosiderin. Liver cells are normal.

Note the rapid destruction of blood during first two weeks, simultaneously with the marked increase of the nucleated reds in the circulating blood (83 to 200 white cells). This period is followed by a gradual regeneration of the blood in the following two months during which time the number of nucleated reds is small (1 to 3). This evident blood regeneration may be due to a compensating hyperactivity of the hematopoietic organs or a period of tolerance during which time the body is able to cope successfully with the poison. Increased blood destruction follows the 80th day, accompanied by an increase in the nucleated red cells. The nucleated reds probably indicate a very active hematopoietic system.

not be held responsible for the icterus. The bile in all four cases was very dark and viscous. Special attention is called to the transient nature of the icterus observed in two of the dogs. In these animals the icterus coincides with periods of very active blood destruction. Furthermore, five out of the six animals that developed icterus were fed on meat, a diet which stimulates blood regeneration. On this diet the number of red corpuscles formed, and possibly the number undergoing disintegration, is greater than on a bread and milk diet, which, as already pointed out, is not as satisfactory for blood regeneration.

Possibly the icterus of these animals was of an obstructive type and hepatogenous in origin due primarily to the viscid bile which led to obstruction in the smaller bile ducts, with consequent absorption of the bile by the hepatic capillaries and without definite liver injury. Another possibility is a functional disturbance of the liver cells, rendering them incapable of dealing with the bile pigment, as normally

The primary rapid blood destruction observed in the dogs chronically poisoned is followed by an evident *blood regeneration*, as seen by the increase in the number of nucleated and reticulated * red corpuscles in the circulating blood and by a polymorphonuclear leukocytosis in most cases. In some animals blood regeneration temporarily overcame blood destruction, followed by a partial return to normal of the pigment volume and the total blood volume. (See Fig. 8.) Then, unless the T.N.T. was discontinued, a recidivation followed the period of active blood regeneration which was associated with a gradual fall in the pigment volume and a reduction in the number of nucleated and reticulated red corpuscles.

All of the animals which had received the poison up to the time of death invariably showed a hyperplastic bone marrow at necrospy in spite of the presence of a very severe anemia.

(*f*) *Influence of Diet.* — On account of the considerable difference in the individual susceptibility to chronic T.N.T. poisoning, it is rather difficult to determine the exact influence of various diets on this intoxication. The number of experiments which would have to be carried out in order to obtain reliable data on this point would of necessity be very large. For this reason, the results obtained in this investigation, while not absolutely conclusive, are at least highly suggestive. It is seen that the animals on a mixed or meat diet seem to be more resistant than the dogs fed on bread and milk. The animals belonging to this latter group as a rule show a more acute and severer anemia, and die sooner.

(*g*) *Importance of Impurities in Crude T.N.T.* — The T.N.T. used for the manufacture of high explosive shells is not a chemically pure substance, although it is a fairly pure product consisting of approximately 99 per cent. 2, 4, 6 trinitrotoluene (T.N.T.).†

Various writers have attributed the toxic action of T.N.T. to the impurities contained therein, among which may be mentioned traces of β and γ trinitrotoluene and especially tetranitromethane.

The results reported in this paper clearly demonstrate that there is no qualitative nor quantitative difference in the pharmacological action of the ordinary T.N.T. obtained from shell-filling plants and chemically pure 2, 4, 6 trinitrotoluene. This latter substance was prepared by Dr. Marcus of this laboratory. Dr. Marcus also tried to isolate the impurities, but suc-

* An increased number of reticulated red corpuscles in the circulating blood is considered by Vogel and McCurdy (25), Lee, Minot, and Vincent (26), and Robertson (27) to be very good evidence of increased activity of the erythroblastic system.

† For literature relating to the manufacture of T.N.T., the reader is referred to Arthur Marshall's "Explosives," J. & A. Churchill, London, England; and G. Smith's "T.N T. Manufacture," New York, Van Nostrand Company, 1918.

ceeded only in obtaining a few milligrams of β trinitrotoluene from 785 gm. of the commercial product. The fact is, therefore, well established that the toxic action of the commercial product is essentially due to 2, 4, 6 trinitrotoluene.

Summary

The results obtained in this work may be briefly summed up as follows:

A condition may be produced in dogs which in the most essential respects very closely resembles T.N.T. poisoning in the human. The symptoms observed are cyanosis, methemoglobinemia, choluria, dyspnea, inco-ordination, and salivation. An anemia appeared in all animals and in six a definite icterus was noted. The blood destruction is due to an injury of the red blood corpuscles leading to increased phagocytosis of these cells in the spleen, liver, and bone marrow (phagocytic anemia). Blood regeneration usually proceeds very slowly after the withdrawal of the poison. The icterus is caused primarily by the enormously increased breakdown of hemoglobin within the phagocytic cells of certain organs and in this respect is hematogenous in origin. Acute yellow atrophy of the liver was never observed in any of the animals.

The toxic action of T.N.T. is essentially due to 2, 4, 6 trinitrotoluene. T.N.T. is changed in the body and is not excreted as such. Reduction and oxidation may take part in this transformation. The reduction products have the same pharmacological action as T.N.T. Trinitrobenzoic acid, the only oxidation product studied, is much less toxic than either T.N.T. or its reduction products. A marked variation in individual and species susceptibility was observed, which is probably dependent on the nature of the change undergone by T.N.T. in the body. A definite tolerance to the poison was never established.

The composition of the diet seems to be a factor influencing the susceptibility of the animals to T.N.T. poisoning.

(*To be continued*)

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BOOK REVIEWS

The Human Motor or the Scientific Foundations of Labor and Industry. By Jules Amar, D.Sc., Director of the Research Laboratory of Industrial Labour at the Conservatoire National des Arts et Métiers, Paris. Translated by Elsie P. Butterworth and George E. Wright. Cloth. Pp. 470 with illustrations and index. London: George Routledge & Sons, Ltd.; New York: E. P. Dutton & Company, 1920.

Before the publication of the present volume in English, Amar's work had already become well-known in this country through his *Physiology of Industrial Organization and the Reemployment of the Disabled*, which appeared in 1919, and in which frequent references were made to his more fundamental work, *The Human Motor*. The present volume is thus received with great interest.

Since the book is addressed to the practical man in industry as well as to the investigator, the author's wisdom is at once evident in beginning with a consideration of the general principles of mechanics most obviously concerned in the movement and work of the human machine. In the subsequent chapters which comprise the first part of the book, the following subjects are considered: the structure of the body; neuromuscular action and the energy exchanges in rest and work, and the relation of diet thereto; human energy, including the consideration of speeds, loads, and effort; fatigue; the internal environment and the physicochemical conditions within the body; and external environment. The second half of the book is devoted to experimental methods of measurement applicable to industrial labor and to the results that have been obtained by these methods.

There is sufficient reason for devoting a large section of the volume to general physical and physiological principles as a matter of convenience for the general reader. Opportunity may thus be taken to emphasize aspects of the subject more directly related to industrial physiology. Amar's treatment of general physiolog-

ical matters bearing upon work is stimulating and suggestive, but it is questionable whether the general reader would obtain an adequate conception of the subject in such a brief treatment.

Any reviewer would perhaps find objections to some views of any writer upon the general subject of physiology, and it should not, therefore, detract from the merit of the work as a whole to criticize certain statements and conceptions. The work quoted on the systolic blood pressure for the different ages does not agree with the general views at the present time as regards normal blood pressure, the average pressure for the ages between 20 and 40 being given by Amar as 170–190 mm. Hg.

As to the chemical phenomena occurring in fatigue, the statements that toxins are produced in the muscle, and that "the blood by circulating more quickly during work washes the poisons out of the tissues and carries them to the suprarenal glands which sècrete adrenalin by which they are neutralized; it oxidizes them itself by the oxygen which it contains," do not represent the best opinions on the subject. Of the same type is the following statement: " . . . sweat is a toxic waste and is produced during fatigue. The poisons which it eliminates in 24 hours would be sufficient to endanger an adult subject. Poisoning sometimes takes place in a hot, humid atmosphere if the sweat has not been able to leave the body." This erroneous view is frequently encountered among people in industry. The statements that the blood of obese subjects is less rich in red corpuscles; that senile decay affects tall people most; that one of the effects of an electrified environment, as after a violent thunder-storm, is anemia; that the application of a moderate current appears to increase the power of muscles for several days; that "chloride of sodium intervenes in the metabolism of the body to protect the proteids," should not be allowed to pass without question. Reference is made to creatinin in connection with muscular activity, but evidently creatin is referred to.

The translation is not altogether good, and as a result unconventional expressions are occasionally used, and the author's meaning is sometimes obscure. As an example of the former, we find in the index a reference to "renal force," with a test for renal force illustrated, the test being a measure of the strength of the lumbar muscles by means of the dynamometer. As an instance of obscure meaning, the following sentence, which occurs in the discussion of nerves, may be cited: "They emanate from determined centers, these centers being cellular, but the 'nervous cell' emits a very long prolongation to the centrifugal function, the cylindric axis, and short appendices, 'the dendrites,' which connect it with the neighboring cells" (p. 99). Moreover, through some mistake of labeling or shading the drawing of the knee joint, an entirely erroneous impression of this structure is given (p. 103).

The author makes several references to differences associated with sex, but does not undertake a general discussion of these differences as bearing upon fitness for various kinds of work. The female suffers in the conventional manner through comparison but it seems a bit unfair to her to draw attention to slight differences in the water content and density of her nervous matter. She is found to possess less muscular strength, and this is more important. In view of more recent results of Martin, however, and the same criticism applies to comparisons of the strength of different races, the effect of occupation probably has not been duly taken into account.

The real contribution of Amar is in pointing out the applications of physiological methods to the study of labor, the results obtained, and those to be expected. His own work has consisted of investigations of pressure and speed of movements by means of Marey tambours and recording devices, following the lead of Imbert in this technic, and of correlating these results with observations upon the oxygen consumption, respiratory rhythm and heart beat. By means of this technic he has determined the work accomplished in relation to the energy expended in several kinds of labor, at various time rates. Interesting and valuable results are given.

Amar's chief incentive is apparently found in the shortcomings of the methods of Taylor and his followers through their failure to take into account the physiological principles concerned in human work. The same criticism has been frequently made, and indeed with justice. Industrial engineers have frequently stated speeds, loads and percentage of time in functional activity in relation to lengths of rest, without taking into account the physiological factors already known, and without making physiological research where such knowledge is inadequate. While Amar must surely convince even the practical engineer of the richness of

this field of investigation he demonstrates, perhaps more than he realizes, its present shortcomings. He is least of all to be criticized in this respect since he is actively working in this field. In making this criticism it is not my purpose to defend any continued neglect upon the part of industrial engineers to ignore physiological facts and methods in their studies, but rather to stimulate greater effort on the part of physiologists.

The two salient deficiencies, in so far as scientific management is concerned, are briefly: first, inadequate methods of determining and stating the work of the human machine; and, secondly, inadequate means of determining the effects of work upon the human machine, *i. e.*, fatigue. In the determination of work, Amar employs the customary methods used in the past. For example, a man uses both hands in filing and makes both vertical and horizontal pressure upon the file. The pressure in both directions is determined in kilograms. He moves the file a certain distance in the horizontal plane. The work which he accomplishes is determined by multiplying the horizontal pressure by the distance through which the file is moved. The downward pressure is disregarded. From a certain standpoint this may be of value — possibly, in comparing the efficiency of the human machine with other types of machines—but from the standpoint of determining quantitatively the physiological activity involved in the work as a basis of reckoning daily functional activity, it is inadequate. Total muscular activity, however, may be inferred from studies on oxygen consumption. This was done in the case of filing. It must be recognized, however, that the oxygen consumption gives no indication of the demands made upon particular muscle groups and, furthermore, that it does not indicate the demands made upon the special senses and nervous system. Our technic must, therefore, be extended to include measurements of the physiological activity of particular muscle groups and other structures concerned in work, if we are to obtain measurements indicative of the demands made upon the human machine. In connection with muscular activity it has long seemed to me that more fruitful results would be obtained by expressing this in terms of tension multiplied by time rather than of weight times distance.

In the matter of determining the effect of work upon the human organism, Amar offers little assistance to the engineer. In the examples given, he recognizes fatigue produced in the work, by irregularities in respiration, pain in a muscle group, unusually high performance in terms of kilogrammeters, and by oxygen consumption, and as we know these are not reliable criteria of fatigue. His contribution to the energy exchanges in the work of an apprentice as compared with a skilled worker is an additional plea for a detailed study of movements in occupation and standardization of the most efficient movements, which, it should be noted, may not be those of the shortest paths or necessarily those requiring the lowest oxygen consumption. The method suggested, which involves a study of the movements of the most efficient workers, is likely to prevent falling into such errors.

Amar indicates the advantages to be gained through proper selection of workmen but does not discuss this aspect of the subject. His classification of men into four types — the digestive, the muscular, the respiratory, and the nervous types, each suited especially to certain types of activity — seems far-fetched; also the statement that subjects with a stronger will have more endurance hardly admits of practical application.

Under external environment there is a brief discussion of atmospheric pressure, the effects of gases and vapors, etc. In connection with high altitudes the work of English investigators is not mentioned, and in connection with caisson sickness the advantage of gradual decompression of the air pressure is not referred to. Moreover, the work referred to in connection with the occurrence of diabetes following exposure to aluminum fumes should be questioned.

Amar is a pioneer and his excellent book should stimulate both the practical man in industry and the laboratory worker to a fuller realization of the fruits which may be reaped through endeavor in this field. — *A. H. Ryan.*